Let's Talk TB

A series on Tuberculosis
A disease that affects over 2 million Indians every year

A Supplement to GP CLINICS®

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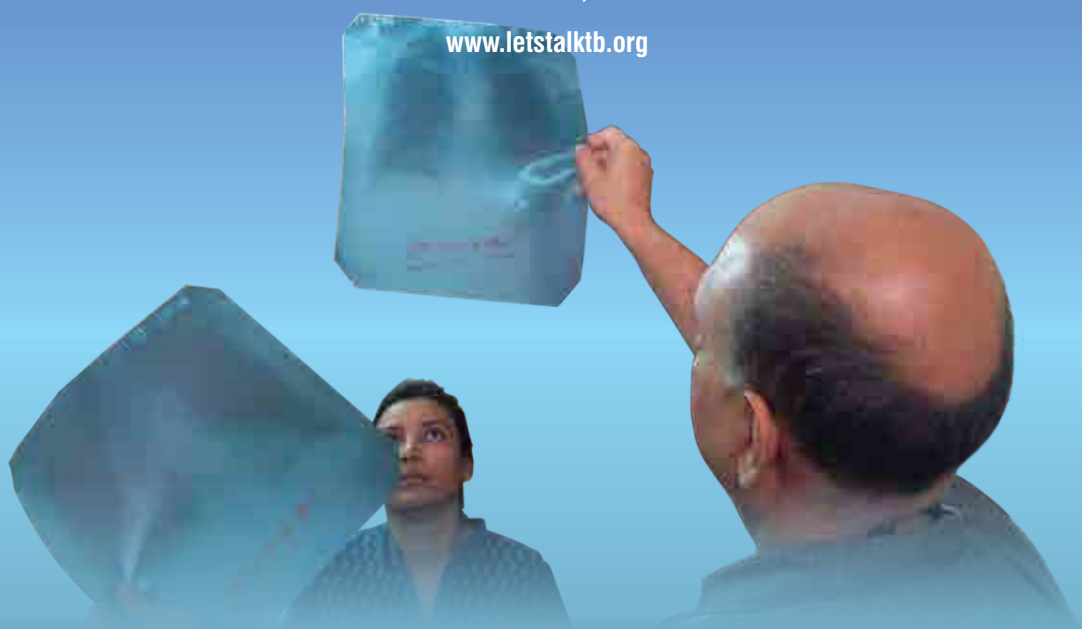

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Madhu's research is mainly focused on improving the diagnosis and treatment of tuberculosis, especially in high-burden countries like India and South Africa. His research is supported by grant funding from the Gates Foundation, Grand Challenges Canada, and Canadian Institutes of Health Research. He has more than 200 peer-reviewed publications. He is recipient of the Union Scientific Prize, Chanchlani Global Health Research Award, and Haile T. Debas Prize. He is a member of the Royal Society of Canada and a Fellow of the Canadian Academy of Health Sciences.

Disclosure: *Madhukar Pai has no financial or industry conflicts. He serves on the Governing Council of IPAQT, and as a consultant for the Bill and Melinda Gates Foundation.*

Editorial

While much progress has been made with tuberculosis (TB) control, the WHO estimates that 10.4 million people developed TB in 2016, and 1.7 million died of TB. India accounts for 25% of the global TB burden, and for a third of the 'missing cases' that do not get diagnosed or notified. The emergence of severe forms of drug-resistance has further complicated the picture.

More than 50% of India's TB patients seek care in the private sector, and private providers and GPs are often the first point of care even for patients treated in the public sector. Unfortunately, private practitioners rarely adhere to national and international standards, and there is plenty of evidence that quality of TB care is often suboptimal. This results in emergence of drug-resistance, and also explains the high TB mortality rate in India.

Without large-scale engagement of the private sector and without improving quality of TB care, it will be impossible to control TB in India. The following 5 strategies, if implemented by all private practitioners, will go a long way in improving outcomes of patients:

- Think TB!
- Actively seek to confirm TB using appropriate sputum tests
- Use the correct drug regimen
- Establish a mechanism for ensuring adherence and treatment completion
- Notify all cases and refer patients with risk factors for drug-resistance

If the above strategies are implemented widely in the private sector, it will improve the quality of TB care in the country, and help control the epidemic.

This supplement to *GP Clinics* is an effort to engage and educate GPs and private practitioners in India, and to share with them the current best practices on TB diagnosis and treatment. It is a compilation of a series of articles published in *GP Clinics* over the past three years.

I am grateful to my co-authors who contributed their valuable expertise and time to this project. I am particularly grateful to Dr Anupam Aggarwal, Editor and Publisher of *GP Clinics*. His enthusiasm and support for TB control is exceptional, and his desire to educate GPs about evidence-based clinical practices is commendable.

Lastly, I am thankful to several partners for their support, including Clinton Health Access Initiative (CHAI), KHPT, The Union, PATH, REACH, World Health Partners, Global Health Strategies, McGill International TB Centre, and McGill Global Health Programs.

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"**Let's Talk TB**", a regular column in **GP Clinics**®, is conceptualised by Dr Anupam Aggarwal, MD and supported by Dr Madhukar Pai, MD to enable physicians to offer TB care that is consistent with the best evidence and standards. This booklet, "**Let's Talk TB**" is a compilation of articles already published in **GP Clinics**.® Each article in the booklet is followed by CME Q&A under the banner CIS CME, which is the **C**linics **I**ndia **S**chool of **C**ontinuing **M**edical **E**ducation.

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Let's Talk TB

A Series on Tuberculosis, A Disease That Affects Over 2 Million Indians Every Year

Diagnosis of Pulmonary Tuberculosis: What Every GP Should Know

Madhukar Pai, MD, PhD—Author and Series Editor

Abstract

India has the highest burden of tuberculosis (TB) in the world, and every GP unit need to consider TB as a differential diagnosis in persons with cough lasting two weeks or more, or with unexplained chronic fever and/or weight loss. Sputum is the most important sample for laboratory testing. Although blood is a popular sample in the Indian private sector, there is no accurate blood test for active TB. Blood-based antibody tests (e.g., IgG/IgMELISA or rapid tests) and interferon-gamma release assays (e.g., TB Gold) are not accu-rate and should not be used for pulmonary TB diagnosis. In fact, the Government of India has recently banned the use of serodiagnostic tests for TB. There are three internationally accepted sputum tests for active TB: sputum smear microscopy for acid-fast bacilli; nucleic acid amplification test (e.g., GeneXpert); and culture. Chest radiography is useful but cannot provide a conclusive diagnosis on its own, and needs to be followed by sputum testing.

Key words: tuberculosis; diagnosis; India; serological tests; test accuracy; case finding

INTRODUCTION

Tuberculosis (TB) remains a problem of enormous magnitude, with nearly 10.4 million new cases and 1.7 million TB deaths every year.[1] Although much progress has been made in TB control, TB incidence is still not declining or not declining as quickly as expected. This is partly because TB patients are not diagnosed and cured quickly enough. When TB patients are not diagnosed and started on anti-TB therapy, they may unknowingly spread their infection to their families and communities - further worsening the epidemic. Thus, early and accurate TB diagnosis is very important - not only for individual patients but also for public health purposes. Early diagnosis can help reduce the amount of lung damage and prevent longterm complications such as bronchiectasis and hemoptysis.

India continues to have the highest number of TB cases in the world, with over 2 million active TB cases every year.[2] Drug resistant TB, including multi-drug resistant disease (MDR), and extensively drug resistant TB (XDR-TB), is a growing concern, especially in hot-spots like Mumbai and urban slums.[3] Studies have shown considerable delays in TB diagnosis, and patients often move from one healthcare provider to another before they are finally diagnosed and put on TB treatment.[4] By the time patients are diagnosed, many have advanced, cavitary disease with substantial lung destruction.

In India, a majority of patients first seek care in the private sector. About half of all TB cases are treated in the private sector in India.[5] This means GPs have a key role to play in early and prompt diagnosis of TB. All GPs must know the key principles and technologies approved for TB diagnosis. They should also know about which tests to avoid because of misleading results and bad consequences for their patients.

CURRENT BEST PRACTICES FOR TB DIAGNOSIS

Given the high rate of TB in India, a GP should actively consider TB in all persons with otherwise unexplained productive cough lasting two weeks or more, or with unexplained chronic fever and/or

Table 1 – Accepted, validated sputum tests for pulmonary TB

Test type or platform	Goal of testing (to detect)	WHO endorsed?	How the test works	Examples of validated commercial versions	Sensitivity	Specificity
Sputum smear microscopy for acid-fast bacilli	Active TB	Yes	Light-emitting diode fluorescence microscopy	Primo Star iLED™ (Carl Zeiss, Oberkochen, Germany) Lumin™ (LW Scientific, Lawrenceville, GA, USA)	>60% (compared to culture)	98% (compared to culture)
Nucleic acid amplification test (NAAT)	Active TB and DST	Yes	Cartridge-Based Automated NAAT is a self-contained and fully automated technological platform that integrates sputum processing, DNA extraction and amplification, TB and MDR-TB diagnosis	Xpert MTB/RIF® [CepheidInc, California, USA]	For active TB: >98% in smear-positive patients and 60 - 70% in smear-negative. For detecting drug-resistance to rifampicin: 95%	For active TB: >98% For detecting drug-resistance to rifampicin: >98%
Liquid culture	Active TB and drug susceptibility testing (DST)	Yes	Fully automated system for mycobacterial liquid culture and drug susceptibility testing	BACTEC MGIT® 960 [BD, Sparks, USA] BacT/ALERT® 3D [bioMérieux, France]	100% in smear-positive cases >75% in smear-negative cases	>99%

weight loss.[6] In addition, GPs should actively screen for TB in clinically high-risk populations such as people living with HIV (even if they are on anti-retroviral treatment), close contacts of TB cases, children who are malnourished, diabetics, and chronic smokers. Among contacts of TB cases, the following groups should be aggressively screened forTB using sputum smears, chest X-rays and molecular tests: persons with symptoms suggestive of TB; children under the age of 5 years; contacts with HIV infection; and contacts of patients with MDR/XDR-TB.

A good diagnostic approach requires collection of the right clinical specimen. For pulmonary TB, sputum is the most important sample for laboratory testing. For several reasons, blood is a popular sample in the Indian private sector.[7] Unfortunately, there is no accepted, valid blood test for pulmonary TB. Therefore, blood samples are of no value. For extrapulmonary TB, it is important to collect specimens from the site of the disease. For example, for pleural effusion, pleural tap and/or biopsy are important. For TB lymphadenitis, it is important to do a lymph node biopsy or fine needle aspiration. For TB meningitis, a spinal tap to collect cerebrospinal fluid (CSF) is mandatory.

All patients (adults, adolescents, and children who are capable of producing sputum) suspected of having pulmonary TB should have at least two sputum specimens submitted for microscopic examination and/or a World Health Organization (WHO) approved molecular test.[6] To reduce drop-outs, where feasible, 2 sputum specimens can be collected on the same day, a minimum of one hour apart.[8] Earlier recommendations required the collection of 3 sputum samples, but the current policy requires 2 specimens for microscopy. It is, however, important that sputum smears are performed in quality-assured laboratories. The public health sector in India has over 13,000 designated microscopy centres (DMCs) where sputum microscopy is done free of charge. GPs can always refer their patients to DMCs for diagnosis, especially if their patients cannot afford private laboratory testing.

There are 3 accepted, validated sputum tests for active TB: sputum smear microscopy for acid-fast bacilli (AFB); molecular or nucleic acid amplification test (NAAT); and culture **(Table 1).** Chest radiography is very widely used in the private sector. It is a useful test and can help quickly identify advanced TB disease (e.g., lung scarring, cavitation, bilateral disease). The problem is that chest X-rays are not specific for the diagnosis of pulmonary TB. Many lung diseases (e.g., chronic bronchitis) and infections (e.g., bacterial pneumonia) can cause radiological abnormalities, and all

Figure 1 – Light-emitting diode (LED) fluorescence microscopy for acid-fast bacilli.

radiological abnormalities are not due to TB, even in a high burden country like India. Also, it can be challenging to differ-entiate between old, inactive TB and currently active TB disease. Therefore, chest radiography cannot provide a conclusive diagnosis on its own, and needs to be followed by sputum testing. Therefore, all persons with chest radiographic findings suggestive of TB should have sputum specimens submitted for microbiological examination (e.g., sputum smears or WHO-approved molecular tests).[6]

At a minimum, GPs should order two sputum smears for AFB in all patients in whom they suspect pulmonary TB. Sputum smears detect highly infectious patients and have high specificity. However, sensitivity of sputum AFB is modest (about 50 - 60%), although higher sensi-tivity can be obtained by performing fluorescence (e.g., auramine) staining and with the use of light-emitting diode (LED) microscopy **(Figure 1).** LED microscopy is approved by the WHO, and is increasingly available in the public sector DMCs. Sputum microscopy generally performs poorly in HIV-infected persons. It is usually of lesser value in young children (who often cannot produce sputum) and in extrapulmonary TB.

NAATs are molecular tests that amplify and detect DNA or RNA of *Mycobacterium tuberculosis.* They are highly specific to TB, and more sensitive than sputum smears and can help diagnose TB rapidly. NAATs can either be in-house ("home-brew") tests or commercial kits. In-house polymerase chain reaction (PCR) is known to produce highly inconsistent results and should be avoided.[9]

There are many commercial NAATs on the market, including validated, US FDA-approved products such as COBAS® Taqman® MTB by Roche, and Amplified *Mycobacterium tuberculosis* Direct [AMTD] by Gen-Probe. These are acceptable but expensive in the Indian private sector. The most important recent advance is the development and WHO endorsement of Xpert® MTB/RIF (Cepheid Inc, Sunnyvale, CA, USA), an automated, cartridge-based NAAT that can detect TB, as well as drug-resistance, within 90 minutes **(Figure 2).**[10] The Xpert MTB/RIF test is based on the GeneXpert® platform. When compared to culture, Xpert has about 88% sensitivity and 98% specificity. For rapid detection of rifampicin resistance, the sensitivity is about 95% and specificity is 98%. So, this test is much more sensitive than sputum smear microscopy, and has great potential to increase the case detection rate.[11] There is growing evidence than Xpert MTB/RIF is quite helpful for rapid diagnosis of extrapulmonary and childhood TB, and WHO is expected to release a policy on this in 2013.[11] WHO released a policy on this in 2013 and approved the use of Xpert MTB/RIF in children and in patients with extra-pulmonary TB.

While Xpert MTB/RIF is a very good technology, high cost remains a big concern for its widespread use. In August 2012, several international donors provided fund-ing to reduce the cost of Xpert MTB/RIF cartridges from $16.86 to $9.98. This reduced price is available for the public sector in 145 high-burden and developing coun-tries. The private sector in high TB burden countries is not eligible for this price. Thanks to the IPAQT initiative (www.ipaqt.org), WHO-endorsed TB tests are now more affordable in the private sector (see later chapter).

If sputum smears and NAATs are negative, and TB is still suspected, cultures are the most sensitive tests avail-

Figure 2 – Xpert® MTB/RIF - a WHO-endorsed automated 2-hour test for TB as well as rifampin resistance.

Figure 3 – Serological, antibody-based TB tests are sold as ELISA kits (top) or rapid tests (bottom) - both versions are banned by the Government of India and should not be used for TB diagnosis

able for TB. TB cultures can be done on solid or liquid media. Liquid cultures are 10% more sensitive than solid cultures and produce results much faster (i.e., within 10 - 14 days). Culture is therefore very useful in diagnosing smear-negative TB, and drug-resistant TB. Cultures can also help isolate non-tuberculous mycobac-terial disease. Previously treated patients and patients who remain sputum smear-positive at completion of intensive phase of TB treatment and patients who have failed, defaulted from, or relapsed following one or more courses of treatment should always be assessed for drug resistance, either using liquid culture or by doing a NAAT such as Xpert MTB/RIF for rifampicin resistance, or line probe assay (LPA) for INH and rifampicin resistance. LPAs are molecular tests (e.g., Genotype MTBDRplus by Hain Life-Science, Germany) that detect mutations that confer drug-resistance and they are endorsed by the WHO. They have excellent accuracy for rifampicin resistance and good accuracy for INH resistance.[12] It is important to note that both culture and LPA require sophisticated laboratories with high degree of qualify assurance.

ROLE OF BLOOD TESTS FOR TB

There are several serological (blood) tests on the market, even though no international guideline recommends their use. Serodiagnostic tests for TB are immunological tests that detect antibody responses to TB antigens in blood/serum samples. They come in two platforms: 1) ELISA tests that detect IgG, IgM and IgA antibodies (e.g., Anda TB and Pathozyme-TB), and 2) rapid strip or card tests (lateral flow assays; immuno- chromatography tests such as "Mycodot" and TB IgG/ IgM) **(Figure 3).** These tests are on the market in at least 17 of the 22 highest TB burden countries, and millions of patients in the private sector undergo serological testing.[13] The situation is particularly bad in India, where over 1.5 million serological TB tests were estimated to be performed in the private sector.[7]

While a simple, rapid blood test for TB will be most helpful, unfortunately, they do not work. TB serological tests are neither accurate nor cost-effective, prompting the WHO to issue a historic strong negative recommendation against their use in 2011.[14] The WHO policy states that, since the "the harms/risks [of commercial serodiagnostic tests] far outweigh any potential benefits (strong recommendation)...these tests should not be used in individuals suspected of active pulmonary or extra-pulmonary TB, irrespective of their HIV status **(Box l).**"[14]

The WHO policy was based on a published meta-analysis that synthesized evidence from 92 studies and concluded that commercial serological tests remain in-consistent and inaccurate, supported only by data of very low quality.[15] A cost-effectiveness study, also considered by WHO, found that serology results in more human suffering, secondary infections, and false-positive diag-noses than sputum smear microscopy, while increasing per-patient costs to the Indian TB control sector.[16]

After this WHO policy, the Indian Revised National

Box 1. Summary of the World Health Organization policy against the use of TB serological tests

- The WHO strongly recommends that commercial serological tests not be used for the diagnosis of pulmonary and extra-pulmonary TB.
- Currently available commercial serodiagnostic tests (also referred to as serological tests) provide inconsistent and imprecise findings.
- There is no evidence that existing commercial serological assays improve patient outcomes, and high proportions of false-positive and false-negative results may have an adverse impact on the health of patients.

Source: World Health Organization[14]

TB Control Programme (RNTCP) published an advisory statement against the use of serological TB tests in India.[17] Subsequently, an expert committee convened by the Drug Controller General of India (DCGI) reviewed the evidence in December 2011, and unanimously recommended a ban on serodiagnostics for TB in India as these tests provide inconsistent and imprecise results. The DCGI recommendations were formally approved and notified in the Gazette of India by the Ministry of Health and Family Welfare on 7th June 2012. This governmental order bans the use, manufacture, sale and import of all TB serodiagnostic test kits in India. The ban applies to all TB serological tests - ELISA as well as rapid diagnostic testsThe ban applies to all TB serological tests - Indian as well as imported. In light of the WHO policy and the Indian Government's ban, it is important for GPs to avoid using all antibody blood tests for TB.[18] Continued use of antibody blood tests is unacceptable and unethical. Indeed, the International Standards for TB Care do not recommend their use.[6]

Blood tests like QuantiFERON-TB Gold In Tube (marketed in India as 'TB Gold" by Qiagen/Cellestis, Australia), T-SPOT.TB (by Oxford Immunotec, UK) and TB Platinum (by Immunoshop India) are called interferon-gamma release assays (IGRAs). These tests do not detect antibodies in the blood. They detect T-cell interferon-gamma response after incubation with TB antigens and measure cellular immune response to TB antigens. They are meant for detection of latent tuberculosis infection (LTBI) and as a potential replacement for the tuberculin skin test (Mantoux test based purified protein derivative).19like the Mantoux test, IGRAs cannot distinguish between latent TB infection and active TB disease.[20-22] In most individuals, *M. tuberculosis* infection is contained initially by host defenses, and infection remains latent. However, latent infection has the potential to develop into active disease at any time. While active TB disease requires 6 months of short-course therapy, latent infection can be treated with a single drug (i.e., isoniazid for 6 - 9 months). Both TST and IGRAs are considered acceptable but imperfect tests for latent TB infection.[23]

With the recent governmental ban on antibody blood tests, laboratories have started replacing them with tests like QuantiFERON-TB Gold. However, tests like TB Gold should not be used to replace serological, antibody-detection tests. IGRAs were never designed for the diagnosis of active TB. In fact, a 2011 WHO policy strongly discourages the use of IGRAs for the diagnosis of active TB in low and middle income countries **(Box 2).**[24] If tests like TB Gold are used for diagnosing active TB, it will result in very high rates of false-positive results and a lot of unnecessary anti-TB drug therapy.[22] This is because an estimated 40% of the Indian population are latently infected[25] and this will result in a large number of positive IGRA results. The same limitation applies to the Mantoux test - it has no value for active TB diagnosis in adults in India. Therefore, GPs should avoid using tests like TB Gold and Mantoux for active TB diagnosis in adults. In children, these tests can provide supportive evidence, along with symptoms, history of contact, smears and chest X-rays.

Box 2. Summary of the World Health Organization policy against the use of interferon-gamma release assays (IGRAs) for active TB*

- IGRAs (and the tuberculin skin test) should not be used in low- and middle-income countries for the diagnosis of pulmonary or extra-pulmonary TB, nor for the diagnostic work-up of adults (including HIV-positive individuals) suspected of active TB in these settings (strong recommendation).
- This recommendation places a high value on avoiding the consequences of unnecessary treatment (high false-positives) given the low specificity of IGRAs (and the TST) in these settings.

Source: World Health Organization[24]
*In India, the most popular IGRA is the QuantiFERON-TB Gold In Tube test, marketed as "TB Gold"

Can serological TB tests be replaced with NAATs on blood samples? NAATs are not recommended for use on blood specimens. It is virtually impossible to detect DNA of MTB in blood samples. NAATs are meant to be used on respiratory samples, and samples from the site of the disease in extra-pulmonary TB. Overall, a key message for all GPs is that there is no valid blood-based test for pulmonary TB. Sputum is the most critical sample to collect and test. GPs must therefore spend time counseling their patients about the need to produce sputum samples for TB testing. Lastly, GPs must avoid starting 6 months of TB therapy without first confirming the disease with one of the validated methods described above.

NOTIFICATION OF TB CASES

On the 7th of May 2012, the Ministry of Health and Family Welfare issued a government order that requires all healthcare providers to notify every TB case to local health authorities (e.g., district or municipal health officers).[26] Healthcare providers include clinical establishments run or managed by the government (including

CLINICAL HIGHLIGHTS

- ❑ All persons with otherwise unexplained productive cough lasting two weeks or more, or with unexplained chronic fever and/or weight loss should be investigated for TB
- ❑ There are no validated, accepted blood-based tests for active TB. Sputum is the ideal specimen to collect for pulmonary TB.
- ❑ All patients suspected of having pulmonary TB should have at least two sputum specimens submitted for microscopic examination and/or a World Health Organization (WHO) approved molecular test such as Xpert MTB/RIF.
- ❑ Chest radiography is useful but cannot provide a conclusive diagnosis on its own, and needs to be fol-lowed by sputum testing.
- ❑ Liquid culture is very useful in diagnosing smear-negative TB, and drug-resistant TB.
- ❑ Drug susceptibility testing must be done on all previously treated patients and patients who remain sputum smear-positive at completion of intensive phase of m treatment and patients who have failed, defaulted from, or relapsed following one or more courses of treatment.
- ❑ There is no clinical role for blood-based antibody tests (e.g., IgG/IgM ELISA or rapid tests) and inter-feron-gamma release assays (e.g., TB Gold). They are not accurate and should not be used for pulmonary TB diagnosis.
- ❑ The Mantoux (tuberculin) skin test cannot distinguish latent TB infection from active TB disease, and has no utility for diagnosing pulmonary TB in adults. It has clinical utility in children, along with other tests such as chest x-ray, smears, and clinical history.
- ❑ All healthcare providers are now required to notify every TB case to local health authorities.

local authorities), private or NGO sectors, as well as individual practitioners (GPs as well as specialists). For the purpose of a case notification, the government order defines a TB case as: 1) a patient diagnosed with at least one sputum specimen positive for AFB, or culture positive forTB bacteria, or RNTCP- endorsed rapid molecular test positive for TB; or 2) a patient diagnosed clinically (without microbiological proof) and given anti-TB drug treatment. The RNTCP has created a web-based portal for notification called NIKSHAY (http://nikshay.gov.in). It is therefore im-portant that all GPs notify TB cases that they diagnose, and fulfill this public health responsibility. ■

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CIS CME–Questions

Diagnosis of Pulmonary Tuberculosis: What Every GP Should Know

Questions

1 Which of the following diagnstics tests is intended for latent tuberculosis infection?

a. Sputum smear microscopy
b. Polymerase chain reaction (PCR)
c. Interferon-gamma release assay (IGRA)
d. ELISA for TB antibodies

2 Which of the following diagnostics tests can be used to diagnose drug-resistant tuberculosis?

a. Sputum smear microscopy
b. liquid culture
c. Interferon-gamma release assay (IGRA)
d. Chest X-ray

3 Which of the following tests are banned by the government of India?

a. Sputum smear microscopy
b. Polymerase chain reaction (PCR)
c. Interferon-gamma release assay (IGRA)
d. Serological (antibody) TB tests

4 The ideal clinical specimen for pulmonary TB diagnosis is:

a. Blood
b. Sputum
c. Urine
d. Tissue

5 Advantages of culture for TB compared to sputum microscopy alone include all of the following EXCEPT:

a. Obtaining a positive culture can allow for drug-susceptibility testing
b. Culture can allow for identification of non-tuberculous mycobacterium species
c. Culture has a higher sensitivity than smear microscopy for diagnosing TB
d. Culture, particularly by liquid media, can be faster than smear microscopy

6 Which of the following statements is FALSE about chest X-rays for TB diagnosis:

a. Chest X-rays have good sensitivity, but poor specificity
b. Chest X-rays can help determine the severity of lung damage
c. Chest X-rays alone is sufficient to diagnose pulmonary TB
d. Chest X-rays can look similar in patients with old, inactive TB and those with currently active TB disease

(See answers on the next page)

CIS CME–Answers

Diagnosis of Pulmonary Tuberculosis: What Every GP Should Know

Questions on the previous page

Answers

1. **The correct answer is (c).** Interferon-gamma release assays (e.g., TB Gold) are meant for the diagnosis of latent TB infection. They should not be used for active TB diagnosis because they cannot distinguish between latent TB and ac¬tive disease. A 2011 World Health Organization (WHO) policy discourages their use for active TB diagnosis.[1]

2. **The correct answer is (b).** Liquid culture can be used to grow *Mycobacterium tuberculosis* and also identify drug resistance (to first and second line drugs). The use of liquid culture is endorsed by the WHO.[2]

3. **The correct answer is (d).** The Indian Government has banned the use, sale and import of all commercial serological (antibody-detection) TB tests. This includes ELISA as well as rapid antibody tests. The ban applies to domestic as well as imported serodiagnostics kits. The ban is based on a WHO policy that strongly recommends against the use of serological, antibody tests for TB.[3] The International Standards for TB Care also discourages the use of serological TB tests.[4]

4. **The correct answer is (b).** Sputum is the best clinical specimen for diagnosis of pulmonary TB. There are no accurate, validated tests for specimens such as blood, urine and tissue.

5. **The correct answer is (d).** Culture is not faster than smear microscopy because even liquid culture needs 10 -14 days for a result to be obtained. Sputum smear results are usually available within 1-2 days.

6. **The correct answer is (c).** Chest X-rays alone is NOT sufficient to diagnose pulmonary TB. It needs to be followed by sputum testing. While chest X-rays have fairly high sensitivity for pulmonary TB, its specificity is low. Many lung conditions and infections can cause chest X-ray abnormalities. So, all patients with chest X-ray abnormalities must be investigated with sputum smears, NAAT and/or culture.

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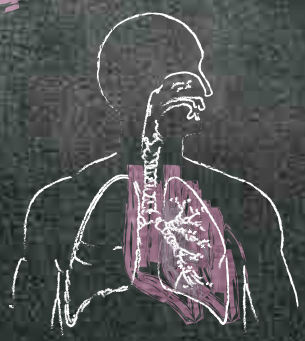
On notice of TB symptoms, immediately rush to your doctor

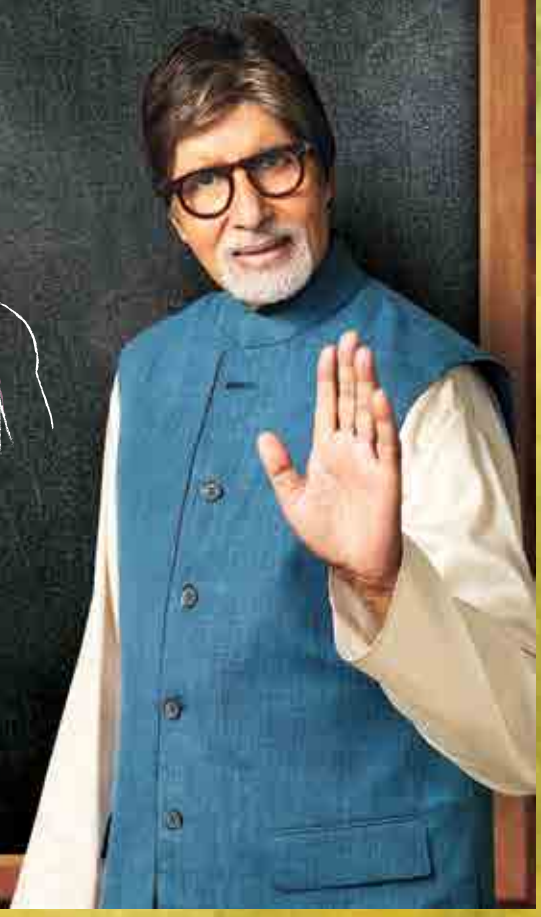


Symptoms of TB

- Cough for more than 2 weeks
- Blood in sputum
- Weakness and fatigue
- Loss of weight
- Reduced appetite
- Evening Temperature

TB HAREGA, DESH JEETEGA.

For more information, consult your doctor.

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MUMBAI MISSION FOR TB CONTROL
Complete your full DOTS course to cure TB successfully
• TB becomes more complex and difficult to treat
• Cost of treatment increases
• Can increase chances of side effects
• Treatment gets prolonged
TB HAREGA, DESH JEETEGA.
For more information, consult your doctor.

Let's Talk TB

A Series on Tuberculosis, A Disease That Affects Over 2 Million Indians Every Year

Diagnosis of Tuberculosis: Importance of Appropriate Specimen Collection

Madhukar Pai, MD, PhD—Author and Series Editor
Pamela Chedore, MLT—Co-author

Abstract

A good diagnostic approach for TB requires collection of the right clinical specimen(s) of adequate quality and quantity. For pulmonary TB, sputum is the most important sample for laboratory testing. Although blood is a popular sample in the Indian private sector, there is no accurate blood test for active TB. For extra-pulmonary TB, it is critical to obtain specimens from the site of disease, and this usually includes collection of tissue (biopsy) and/or body cavity fluids from the suspected disease site. For childhood TB diagnosis, sputum can be collected from older children. In young children, fasting gastric aspirates are the routinely collected samples. For latent TB infection diagnosis, there are two main options – interferon-gamma release assays which require venous blood samples, or the tuberculin skin test (Mantoux), which is an intra-dermal skin test. In all the above situations, clear instructions on specimen collection should be provided to patients as well as to laboratories and clinics. Quality of specimens can often have a big impact on test results, and every effort should be made to ensure quality in specimen collection, transport and processing.

Key words: tuberculosis; diagnosis; sputum specimens; sample collection methods

INTRODUCTION

In a previous article in this series, the best practices for pulmonary tuberculosis (TB) diagnosis were described.[1] This article provides additional information on specimen collection for laboratory diagnosis. A good diagnostic approach for TB requires collection of the right clinical specimen and use of the appropriate laboratory test. All clinicians, therefore, should have basic knowledge about the types of specimens that must be collected, and should be able to provide clear instructions to their patients on how to provide such specimens at the laboratory, or in the clinic, if samples are collected and then transported to laboratories.

The specimen type is decided by the site of disease, purpose of testing or the patient population. The following four distinct sites/purposes should guide specimen collection (**Table 1**):

- Active, pulmonary tuberculosis
- Active, extra-pulmonary tuberculosis (multiple sites are possible)
- Childhood tuberculosis
- Latent tuberculosis infection

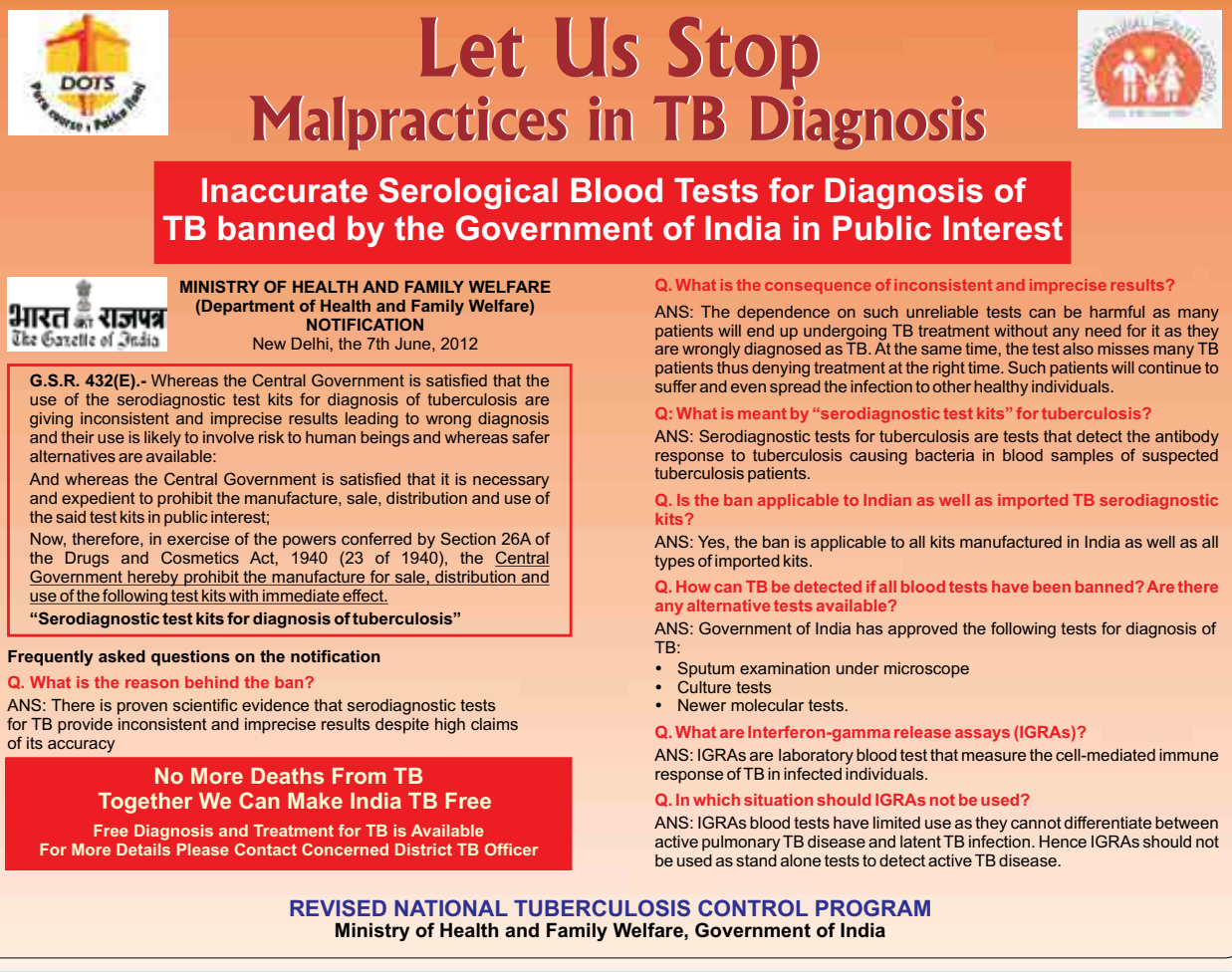
SPECIMENS FOR ACTIVE, PULMONARY TB

For pulmonary TB, sputum is the single most important sample for laboratory testing. For several reasons, blood is a popular sample in the Indian private sector.[2] Unfortunately, there is no accepted, valid blood test for pulmonary TB. Blood is not the ideal sample for any of the accepted TB testing technologies, namely, smear microscopy for acid-fast bacilli (AFB), culture, and molecular tests (e.g., polymerase chain reaction [PCR]). In fact, blood-based, serological, antibody-detection tests for TB (e.g., IgM/IgG anti-

Table 1 – The specimen type is decided by the site of disease or purpose of testing or patient population

Site, purpose, or patient population	Specimen of choice	Comments
Active, pulmonary TB	Sputum (spontaneous or induced)	- Sputum must be produced deep from within the lungs - Saliva is not acceptable - At least two sputum samples must be collected - Blood is not acceptable as a sample for active, pulmonary TB - Rarely, bronchoalveolar lavage (BAL) is used to collect lung secretions – this requires expertise and hospital care
Active, extrapulmonary TB		
TB lymphadenitis	Lymph node aspirate or biopsy	- Requires needle aspiration and/or excision biopsy - Samples are then sent for smears for AFB, liquid culture, molecular (PCR) tests, and histopathological examination - Histopathology and liquid culture are the most important tests; PCR may help, if positive
Pleural effusion (TB pleuritis)	Pleural fluid and pleural biopsy	- Requires pleural tap and/or biopsy - Samples are then sent for pleural fluid analysis, smears for AFB, liquid culture, molecular (PCR) tests, and histopathological examination; pleural fluid adenosine deaminase (ADA) or interferon-gamma is often helpful - Histopathology and liquid culture are the most important tests; PCR may help, if positive
Ascites (abdominal TB)	Ascitic fluid and peritoneal biopsy	- Requires ascitic tap and/or biopsy - Samples are then sent for smears for AFB, ascitic fluid analysis, liquid culture, molecular (PCR) tests, and histopathological examination; ascitic fluid ADA or interferon-gamma is often helpful - Histopathology and liquid culture are the most important tests; PCR may help, if positive
TB meningitis	Cerebrospinal fluid (CSF)	- Requires spinal tap for CSF collection - Samples are then sent for smears for AFB, CSF analysis, liquid culture, molecular (PCR) tests - Liquid culture of CSF along with CSF analysis is most important; PCR may help, if positive
Bone and joint TB	Bone/synovial tissue via biopsy	- Histopathology and liquid culture are the most important tests; PCR may help, if positive
Urinary tract and kidneys TB	Urine and tissue via biopsy	- Histopathology and liquid culture are the most important tests; PCR may help, if positive
Genito-urinary tract TB	Tissue via biopsy (e.g., endometrial tissue in women)	- Menstrual blood is not ideal; it is important to collect endometrial tissue - Histopathology and liquid culture are the most important tests; PCR may help, if positive
Childhood TB	Sputum in older children; in younger children, gastric aspirates	See Table 2 for additional options and comments
Latent TB infection	Whole blood for interferon-gamma release assays (IGRAs); or Mantoux intra-dermal skin test	- IGRAs are only meant for latent TB infection – they cannot separate latent infection from active disease - Mantoux skin test must be correctly performed and read

Box 1. Frequently asked questions about the Indian governmental ban on TB serological tests, published in several Indian newspapers in December 2012 in India



Let Us Stop
Malpractices in TB Diagnosis

Inaccurate Serological Blood Tests for Diagnosis of TB banned by the Government of India in Public Interest

भारत का राजपत्र
The Gazette of India

MINISTRY OF HEALTH AND FAMILY WELFARE
(Department of Health and Family Welfare)
NOTIFICATION
New Delhi, the 7th June, 2012

G.S.R. 432(E).- Whereas the Central Government is satisfied that the use of the serodiagnostic test kits for diagnosis of tuberculosis are giving inconsistent and imprecise results leading to wrong diagnosis and their use is likely to involve risk to human beings and whereas safer alternatives are available:

And whereas the Central Government is satisfied that it is necessary and expedient to prohibit the manufacture, sale, distribution and use of the said test kits in public interest;

Now, therefore, in exercise of the powers conferred by Section 26A of the Drugs and Cosmetics Act, 1940 (23 of 1940), the Central Government hereby prohibit the manufacture for sale, distribution and use of the following test kits with immediate effect.

"Serodiagnostic test kits for diagnosis of tuberculosis"

Frequently asked questions on the notification

Q. What is the reason behind the ban?

ANS: There is proven scientific evidence that serodiagnostic tests for TB provide inconsistent and imprecise results despite high claims of its accuracy

No More Deaths From TB
Together We Can Make India TB Free
Free Diagnosis and Treatment for TB is Available
For More Details Please Contact Concerned District TB Officer

Q. What is the consequence of inconsistent and imprecise results?

ANS: The dependence on such unreliable tests can be harmful as many patients will end up undergoing TB treatment without any need for it as they are wrongly diagnosed as TB. At the same time, the test also misses many TB patients thus denying treatment at the right time. Such patients will continue to suffer and even spread the infection to other healthy individuals.

Q: What is meant by "serodiagnostic test kits" for tuberculosis?

ANS: Serodiagnostic tests for tuberculosis are tests that detect the antibody response to tuberculosis causing bacteria in blood samples of suspected tuberculosis patients.

Q. Is the ban applicable to Indian as well as imported TB serodiagnostic kits?

ANS: Yes, the ban is applicable to all kits manufactured in India as well as all types of imported kits.

Q. How can TB be detected if all blood tests have been banned? Are there any alternative tests available?

ANS: Government of India has approved the following tests for diagnosis of TB:

- Sputum examination under microscope
- Culture tests
- Newer molecular tests.

Q. What are Interferon-gamma release assays (IGRAs)?

ANS: IGRAs are laboratory blood test that measure the cell-mediated immune response of TB in infected individuals.

Q. In which situation should IGRAs not be used?

ANS: IGRAs blood tests have limited use as they cannot differentiate between active pulmonary TB disease and latent TB infection. Hence IGRAs should not be used as stand alone tests to detect active TB disease.

REVISED NATIONAL TUBERCULOSIS CONTROL PROGRAM
Ministry of Health and Family Welfare, Government of India

dawp 17137/13/0001/1213

(reproduced with permission from Central TB Division, Ministry of Health and Family Welfare).

bodies using ELISA and rapid tests) have been strongly discouraged by the World Health Organization (WHO), and banned in 2012 by the Government of India.[3]

Although there are blood-based tests for latent TB infection (e.g., interferon-gamma release assays such as QuantiFERON TB-Gold – marketed in India as "TB Gold" by Qiagen), these tests have no value for active pulmonary TB diagnosis and should be avoided.[4,5] Recently, the Revised National TB Control Programme (RNTCP) in India published frequently asked questions (FAQs) on the ban on serology in leading Indian newspapers (**Box 1**).

All patients (adults, adolescents, and older children who are capable of producing sputum) suspected of having pulmonary TB should have at least two sputum specimens submitted for microscopic examination and/or a World Health Organization (WHO) approved molecular test (e.g., Xpert MTB/RIF by Cepheid Inc.) or culture (e.g., MGIT by BD Diagnostics).[6] To reduce drop-outs, where feasible, 2 sputum specimens can be collected on the same day, a minimum of one hour apart.[7] Earlier recommendations required the collection of 3 sputum samples, but the current policy requires 2 specimens for microscopy, provided microscopy is done with quality assurance.

All specimens must be collected in sterile, leak-proof, laboratory-approved containers, labeled on the side with the patient's name and the date of collection

Figure 1 – Sputum samples are usually thick and mucoid with varying color

and accompanied by a carefully completed requisition form providing the patient's name and age, the physician's name and address, the date and time of collection, whether the specimen is diagnostic or follow-up and the specimen type and site. As much as possible, specimens collected for initial diagnosis should be obtained before the initiation of anti-TB therapy.

Sputum can be collected in one of two ways: spontaneous expectoration, and sputum induction. Spontaneous expectoration requires the patient to cough up a sputum sample from the lung without any assistance. If the patient is unable to produce a sample, then sputum induction can be done to stimulate a deep cough. Sputum induction is usually done by asking the patient to inhale nebulised hypertonic saline in a sputum induction chamber that ensures biosafety. Sometimes, bronchoalveolar lavage (BAL) may be necessary to collect samples from the lung. BAL is performed in a hospital with the patient sedated. A 5 ml portion of the lavage fluid may be submitted for TB testing and a post-bronchoscopy sputum specimen should also be collected and submitted.

Sputum is a respiratory secretion originating from deep within the lungs. Unless properly instructed, patients may provide saliva samples instead of sputum. Thus, all patients should be instructed on the difference between sputum and saliva or nasopharyngeal secretions and the necessity for a deep, productive cough. The following instructions should be provided to patients:[8]

- The importance of sputum examination for diagnosis or follow-up of pulmonary TB;
- The fact that TB is usually a curable disease and that if their test is positive they will receive treatment (available free anywhere in India via the RNTCP);
- How to open and completely close the screw-capped containers without touching the inside;
- The need for collecting 1 to 2 teaspoons of real sputum, not saliva;
- To first wash their mouth out with cooled, boiled water to avoid food particles in the specimen;
- How to produce good sputum (i.e., the patient is relaxed and seated. They cover their mouth with a tissue and after several repeated deep inhalations and exhalations of breath they cough the sputum up into their mouth from as deep inside the chest as possible. They then carefully spit the sputum into the opened container and close it);
- If possible, to collect the first specimen in the early morning since sputum and bacilli accumulate in the lungs overnight;
- To expectorate sputum specimens in the open air or in a well ventilated area;
- How to avoid contamination of the exterior of the container (i.e., by carefully spitting and closing the container);
- To wash their hands with soap and water after specimen collection;
- How to safely deliver the morning sputum to the laboratory as soon as possible after it is produced; and
- The need for at least two sputum specimens to facilitate diagnosis.

A good specimen should be approximately 5 ml. All samples should be inspected by clinic staff before sending to the laboratory. Sputum is usually thick and mucoid and color may vary (white, green, or bloody) (**Figure 1**). It may be fluid and contain pieces of purulent material. Clear saliva or nasal discharge is not a suitable specimen (**Figure 2**). Induced sputum samples are usually watery, but are acceptable since they come from the lungs. The accompanying form should state 'induced sputum'. Specimens should be equal in volume to about two teaspoons of material. If the specimen is inadequate the patient must be asked to repeat the procedure until an adequate quantity and quality of specimen is obtained.

Suitable sputum containers should be wide-mouthed, sterile, disposable, translucent and leak-proof with a screw cap and a space for labeling on the side. Alternatively, if the specimen is for smear and culture, it can be expectorated directly into a sterile 50 ml conical, screw-capped laboratory tube. Re-usable glass, screw-capped universal containers may be used if the laboratory has a facility for sterilising and cleaning the vials for re-use. All containers must be labeled with the patient's name and the date of specimen collection in indelible ink on the side of the container, not on the cap.

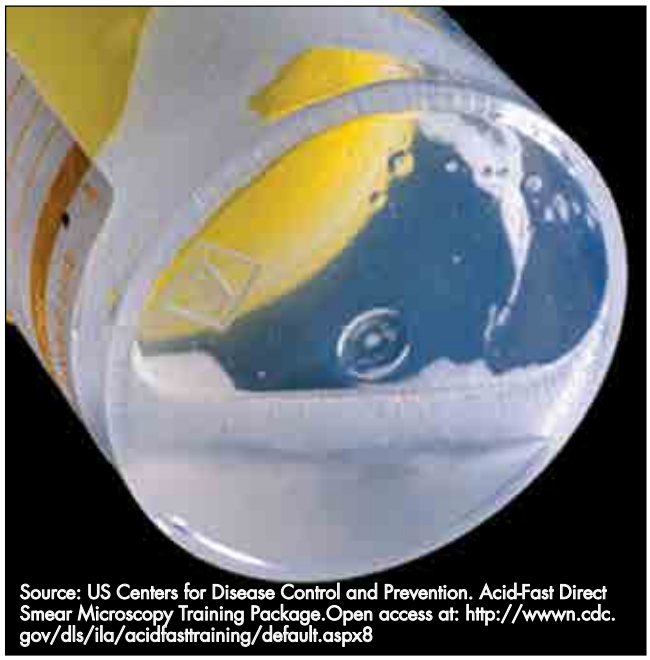

Source: US Centers for Disease Control and Prevention. Acid-Fast Direct Smear Microscopy Training Package.Open access at: http://wwwn.cdc.gov/dls/ila/acidfasttraining/default.aspx8

Figure 2 – Saliva is not an acceptable specimen for TB diagnosis

Sputum samples must be collected and transported safely so as to avoid the risk of infection to clinic and lab staff or other handlers. Containers must be capped firmly and any sputum noticed on the outside of the container must be wiped clean with bleach. Specimens should be packed upright in accordance with national requirements for transportation. Forms must be kept separate from the specimens to avoid contamination. Specimens should be transported to the laboratory as soon as possible and if there is a delay of > 2hours, they should be refrigerated.

The diagnosis of multi-drug resistant TB (MDR-TB) is usually based on molecular tests (e.g., Genotype MTBDRplus by Hain LifeScience; or Xpert MTB/RIF by Cepheid) or liquid cultures (e.g., MGIT by BD or BacT Alert by bioMerieux) done on sputum samples.

SPECIMENS FOR ACTIVE, EXTRA-PULMONARY TB (EPTB) DIAGNOSIS

EPTB can occur in many sites, the most common sites being lymph nodes, pleural, abdominal and meningeal sites. Other sites can include bone and joints, kidneys, genitourinary tract, and pericardial. EPTB cannot be diagnosed with sputum or blood specimens. It is critical to make an effort to collect tissue and fluids from the site of the disease. This may require surgical expertise and referral to a center where biopsies can be done safely. **Table 1** shows the various types of specimens for different disease sites. The most common diagnostic tests on EPTB samples are:

- Smear for acid-fast bacilli (AFB);
- Liquid culture on fluids or tissue samples;
- Molecular (PCR) tests (e.g., Xpert MTB/RIF® by Cepheid);
- Histopathological examination of biopsy tissue;
- Adenosine deaminase (ADA) or free interferon-gamma levels in sterile fluids such as pleural, peritoneal and pericardial fluids.

Smears are often negative in EPTB specimens because of the low numbers of AFB. Liquid cultures and histopathology results are therefore critical. Molecular/PCR tests are helpful if positive. However, if PCR tests are negative, EPTB cannot be ruled out. This is because molecular tests for EPTB are highly specific, but sensitivity is not very high.[9-11] It is important to note that molecular tests for EPTB should not be performed on venous blood specimens. They should be used on specimens from the site of the disease.

SPECIMENS FOR CHILDHOOD TB

Table 2 provides a summary of various specimen collection methods for pediatric TB, and the perceived problems and/or benefits of each.[12] While older children may be able to cough up sputum samples, this is very difficult in young children since they tend to swallow sputum rather than expectorate them. In young children (<7-8 years of age), the routine specimens collected are two to three fasting gastric aspirates (gastric juice aspirate). However, the collection of 2-3 fasting, early morning gastric aspirate specimens is cumbersome and usually requires hospitalization. The following are basic guidelines for collecting gastric aspirates: 1) Specimens are collected after the child has fasted for eight to ten hours and, preferably, while the child is still in bed; 2) Specimens are usually collected daily for three days.

There is no adequate gold standard test for childhood TB, and diagnosis requires multiple tests.[13] Smears for AFB are often negative because of the low numbers of AFB in childhood TB. Therefore, liquid culture and molecular tests may be most helpful, along with signs, symptoms, chest radiology, evidence of TB infection (e.g., positive Mantoux skin test), and history of contact with active TB. The diagnosis and management of childhood TB will be covered in a future article in this series.

SPECIMENS FOR LATENT TB INFECTION (LTBI)

The diagnosis and management of latent TB infection will be covered in a future article in this series. Briefly, the goal of testing for latent TB infection is to identify individuals (e.g., close contacts of active TB cases) who are at increased risk for the development of active TB

Table 2 – Specimen collection methods for childhood TB[12]

Specimen collection method	Problems/Benefits	Potential clinical application
Sputum	Not feasible in very young children; Assistance and supervision may improve the quality of the specimen	Routine sample to be collected in children >7yrs of age (all children who can produce a good quality specimen)
Induced sputum	Increased yield compared to gastric aspirate; No age restriction; Specialized technique, which requires nebulization and suction facilities; Use outside hospital setting not studied; Potential transmission risk	To be considered in the hospital setting on an in- or out-patient basis
Gastric aspirate	Difficult and invasive procedure; Not easily performed on an outpatient basis; Requires prolonged fasting; Sample collection advised on 3 consecutive days	Routine sample to be collected in hospitalized patients who cannot produce a good quality sputum specimen
Nasopharyngeal aspiration	Less invasive than gastric aspirate; No fasting required; Comparable yield to gastric aspirate	To be considered in primary health care clinics or on an outpatient basis
String test	Less invasive than gastric aspirate; Tolerated well in children >4 years; Bacteriologic yield and feasibility requires further investigation	Potential to become the routine sample collected in children who can swallow the capsule, but cannot produce a good quality sputum specimen
Bronchoalveolar lavage	Extremely invasive	Only for use in patients who are intubated or who require diagnostic bronchoscopy
Urine/Stool	Not invasive; Excretion of *M. tuberculosis* well documented	To be considered with novel sensitive bacteriologic or antigen-based tests
Blood/Bone marrow	Good sample sources to consider in the case of probable disseminated TB	To be considered for the confirmation of probable disseminated TB in hospitalized patients
Cerebrospinal fluid (CSF)	Fairly invasive; bacteriologic yield low	To be considered if signs of tuberculous meningitis
Fine needle aspiration biopsy (FNAB)	Minimally invasive using a fine 23G needle; excellent bacteriologic yield,	Procedure of choice in children with superficial lymphadenopathy; minimal side-effects

Adapted from: Marais BJ. Pai M. Specimen collection methods in the diagnosis of childhood tuberculosis. *Indian J Med Microbiol* 2006;24:249-251.[12]

and therefore would benefit from treatment of latent TB infection (e.g., isoniazid for 6-9 months, after active TB is ruled out). Only those who would benefit from treatment should be tested, so a decision to test presupposes a decision to treat if the test is positive.

There are two accepted tests for identification of LTBI: the tuberculin skin test (TST) and the interferon gamma release assay (IGRA). As with the TST, IGRAs are surrogate markers of *Mycobacterium tuberculosis* infection and indicate a cellular immune response to *M. tuberculosis*.[14] In other words, both tests provide indirect evidence that the patient has been sensitized to *Mycobacterium tuberculosis* in the past. Neither test proves that the patient has current active TB disease, and should not be used to diagnose active TB.

IGRAs require blood samples, while the TST is an intra-dermal skin test (Mantoux technique). For IGRAs such as QuantiFERON-TB Gold®, blood must be collected in special antigen-coated tubes and shaken after blood collection to ensure that blood comes into contact with TB-specific antigens. Blood tubes are then incubated overnight and supernatants are then assayed via ELISA for interferon-gamma levels. It is important to strictly follow manufacturers' recommendations on IGRAs. Delays in incubating the blood can cause loss in sensitivity and increase the rate of indeterminate results.

TST should be performed using the Mantoux technique which consists of intradermal injection of tuberculin material (0.1 ml of purified protein derivative (2TU of PPD RT23)) on the inner surface of the forearm. A clear, raised wheal of 6-10 mm diameter should appear

CLINICAL HIGHLIGHTS

❑ A good diagnostic approach for tuberculosis (TB) requires collection of the right clinical specimen of good quality and quantity, and use of the appropriate laboratory test.

❑ All clinicians, therefore, should have basic knowledge about the types of specimens that can be collected, and should be able to provide clear instructions to their patients on how to provide such specimens.

❑ The specimen type is decided by the site of disease or purpose of testing or patient population.

❑ Sputum is the ideal specimen to collect for pulmonary TB. There are no validated, accepted blood-based tests for active TB.

❑ All patients suspected of having pulmonary TB should have at least two sputum specimens submitted.

❑ All patients should be instructed on the difference between sputum and saliva or nasopharyngeal secretions and the necessity for a deep, productive cough.

❑ Extrapulmonary TB (EPTB) can occur in many sites, the most common being lymph nodes, pleural, abdominal and meningeal sites. EPTB cannot be diagnosed with sputum or blood specimens. It is critical to make an effort to collect tissue and fluids from the site of the disease. This may require surgical expertise and referral to a center where biopsies can be done safely.

❑ Childhood TB can pose many challenges for specimen collection. While older children may be able to cough up sputum samples, this is very difficult in young children. In young children (<7-8 years of age), the routine specimens collected are two to three fasting gastric aspirates (gastric juice aspirate).

❑ There are two accepted tests for identification of latent TB infection (LTBI): the tuberculin skin test (TST) and the interferon gamma release assay (IGRA). IGRAs require blood samples, while the TST is an intra-dermal skin test (Mantoux technique).

when the PPD is slowly injected into the skin. The results should be read 48-72 hours after administration, by a trained professional. Transverse induration should be measured in mm. Redness (erythema) is not measured.An induration of 10 mm or more is usually considered positive for TB infection.

SOME COMMON SPECIMEN-RELATED ERRORS IN THE INDIAN CONTEXT

As mentioned previously, the most common error in the Indian context is use of blood (instead of sputum) as the specimen for active pulmonary and extra-pulmonary TB diagnosis. Indian labs not only perform blood tests like serology for TB, they also perform PCR tests on blood samples. These practices are unscientific and need to be discouraged. The exception would be use of blood culture or PCR for the diagnosis of disseminated TB in children or immune-suppressed persons. The more recent use of IGRAs like TB Gold for active TB is another cause for concern that will need to be addressed by clinicians and laboratory professionals in India.

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CIS CME–Questions

Diagnosis of Tuberculosis:
Importance of Appropriate Specimen Collection

Questions

1. **What is the ideal location for sputum collection?**
   a. Inside the doctor's clinic
   b. Inside the laboratory
   c. Outdoors or in a well ventilated area
   d. The patient's bathroom with the door closed

2. **Which of the following tests requires a blood sample for the diagnosis of active pulmonary TB?**
   a. Sputum smear microscopy
   b. Liquid culture
   c. Interferon-gamma release assay (IGRA)
   d. None of the above

3. **Which of the following constitutes a good sample for sputum microscopy?**
   a. 5 ml of muco-purulent sputum
   b. 5 ml of clear saliva
   c. 2 ml of sputum in a washed food container
   d. All of the above

4. **For a two year old child with suspected TB, the best clinical specimen for pulmonary TB diagnosis is:**
   a. Blood
   b. Sputum
   c. Gastric aspirate
   d. Bronchoalveolar lavage (BAL)

5. **What is the minimum recommended number and timing of specimens for the diagnosis of pulmonary TB?**
   a. Three early morning sputum specimens
   b. Two sputum specimens collected one hour apart
   c. Three sputum specimens taken on the same day
   d. One early morning sputum plus one blood sample

6. **Which of the following specimens should be rejected by the culture laboratory?**
   a. An unlabeled sputum specimen
   b. A lymph node received in fixative
   c. A specimen received without a request form
   d. All of the above

7. **In a woman with infertility, suspected to have genito-urinary TB, which of the following specimens is important for diagnosis?**
   a. Venous blood
   b. Menstrual blood
   c. Endometrial tissue
   d. Sputum

(See answers on the next page)

CIS CME–Answers

Diagnosis of Tuberculosis:
Importance of Appropriate Specimen Collection
Questions on the previous page

Answers

1. **The correct answer is (c).** Sputum expectoration can release infectious aerosols, which are diluted in the open-air or a well ventilated room and are inactivated by UV light in the outdoors.

2. **The correct answer is (d).** There is no approved blood test for the diagnosis of active pulmonary TB. IGRAs are tested on blood but only give information on latent TB infection, not active disease.[1]

3. **The correct answer is (a).** Sputum quality and quantity are essential features of a good specimen for TB testing. Five ml of muco-purulent specimen collected in a sterile laboratory approved container is the ideal specimen for sputum microscopy for TB.

4. **The correct answer is (c).** Young children cannot expectorate sputum but it is often swallowed overnight. The best specimen is, therefore, a series of two to three consecutive, fasting gastric aspirates.[2]

5. **The correct answer is (b).** The minimum requirement for sputum testing is two specimens taken one hour apart.[3] Previously three consecutive early morning sputum samples were recommended but research has shown that the 3rd sample does not add much to the overall yield (and can increase the risk of patient drop-out).[4]

6. **The correct answer is (d).** Specimens that are unlabeled or do not have a properly filled out form, are rejected by the laboratory. Fixatives, such as formalin, will inactivate any micro-organisms in a tissue sample, therefore, making it unsuitable for culture.

7. **The correct answer is (c).** Endometrial issue for culture and histopathology is critical for diagnosing genito-urinary tract TB. Blood (venous or menstrual) is not the appropriate sample as it is very difficult to isolate *M. tuberculosis* or detect MTB DNA in such samples.

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Interpretation of Chest X-rays in Tuberculosis

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Abstract

Every GP in India will need to consider TB as a differential diagnosis in persons with cough lasting two weeks or more, or with unexplained chronic fever and/or weight loss. Chest radiography is very widely used in India. Chest x-rays serve as an invaluable adjunct in the diagnosis and follow-up of TB. However, TB may mimic other diseases on x-rays, and non TB conditions may look like TB. Thus, chest x-rays are neither specific nor sensitive, and so remain a supplement to microbiological tests such as microscopy, PCR and culture. Treatment of TB purely on the basis of x-rays can result in significant over-treatment with adverse consequences for patients. Therefore, all persons with chest radiographic findings suggestive of TB should have sputum specimens submitted for microbiological examination. This article provides a series of x-rays that serve to educate the provider about radiological interpretation of TB and common pitfalls and errors in interpretation.

Key words: tuberculosis, diagnosis, radiology, chest x-rays

INTRODUCTION

The definitive diagnosis of active pulmonary TB is made by sputum microscopy, rapid molecular tests (e.g., PCR) and culture.[1,2] Chest x-rays serve as an invaluable adjunct in the diagnosis and follow-up of this disease. In the event of negative cultures, it can provide the only way to suspect active disease and is useful in the assessment of treatment response. However, TB may mimic other diseases on x-rays, and non TB conditions may look like TB. Thus chest x-rays are neither specific nor sensitive, and so remain a supplement to microscopy, PCR and culture.[1,2]

The radiologic appearance of TB reflects the host response to infection. TB infects the lung by inhalation of droplets from a person with active disease. In 90% of patients, the infection remains latent. In approximately 5% it progresses to active disease within a short period, causing primary disease. In the remaining 5%, it may remain latent for many years before reactivating, causing reactivation, or post primary disease. The radiologic appearance of primary versus reactivation TB is very different. Most of the cases you will see in your practice are reactivation disease. Most children develop primary disease and their radiological presentation can be different from adults (radiology in children is not covered in this article).

TB can involve the pulmonary parenchyma, interstitium, pleura, pericardium and bone, each resulting in a different radiologic picture. In general, the presence of upper-lobe opacities, cavities, a unilateralpleural effusion, and hilar or mediastinal lymphadenopathy may be the most useful radiological markers of pulmonary TB.[3,4]

The following chest x-rays (CXR's) illustrate the different radiologic manifestations of TB. There are also cases that are not TB, but look like TB. Finally, there are cases that look like other diseases but eventually turned out to be TB. HIV infection is the most common reason for atypical radiographic appearance in TB patients. The altered ra-

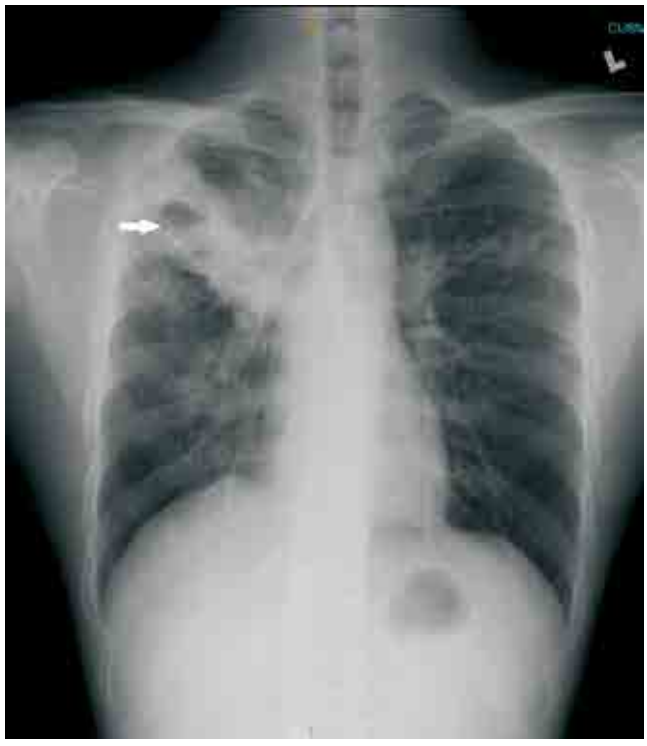

Figure 1 – Classical picture of active pulmonary TB

diographic appearance of pulmonary TB in patients with HIV is due to compromised immunity.

Quality of radiographs is important to consider, and films should be read carefully as inter- and intra-reader variations are common.[5] All x-rays must be interpreted with relevant clinical and laboratory data.

CLASSICAL TB

In **Figure 1** you can see the classical picture of active pulmonary TB. There is bilateral airspace disease, much more prominent in the right lung. There are also multiple cavities in the RUL (right upper lobe). Although this is typical of TB, if the history was an acute one, i.e., a 5 day history of cough and high fever, the diagnosis would more likely be an aerobic bacterial infection, i.e., staphylococcus or a gram negative pneumonia. CXR's must always be interpreted in light of the clinical history!

THE LORDOTIC CXR

The lordotic CXR is useful in visualizing the apical structures of the lung. Because of the overlap of clavicle, the first rib and posterior ribs, lesions at the apex can be missed. In the lordotic view, the x-ray beam is angled up through the chest, as shown in **Figure 2**, shifting anterior structures (clavicle and first rib, superiorly), affording a better view of the apices

In **Figure 3a**, the patient was suspected of having a lesion behind the left 2nd rib (arrow). A lordotic CXR (**Figure 3b**) confirmed this to be a cavitary lesion, and sputum sample grew TB on culture.

MINIMAL TB

Early stages of TB can cause minimal radiologic

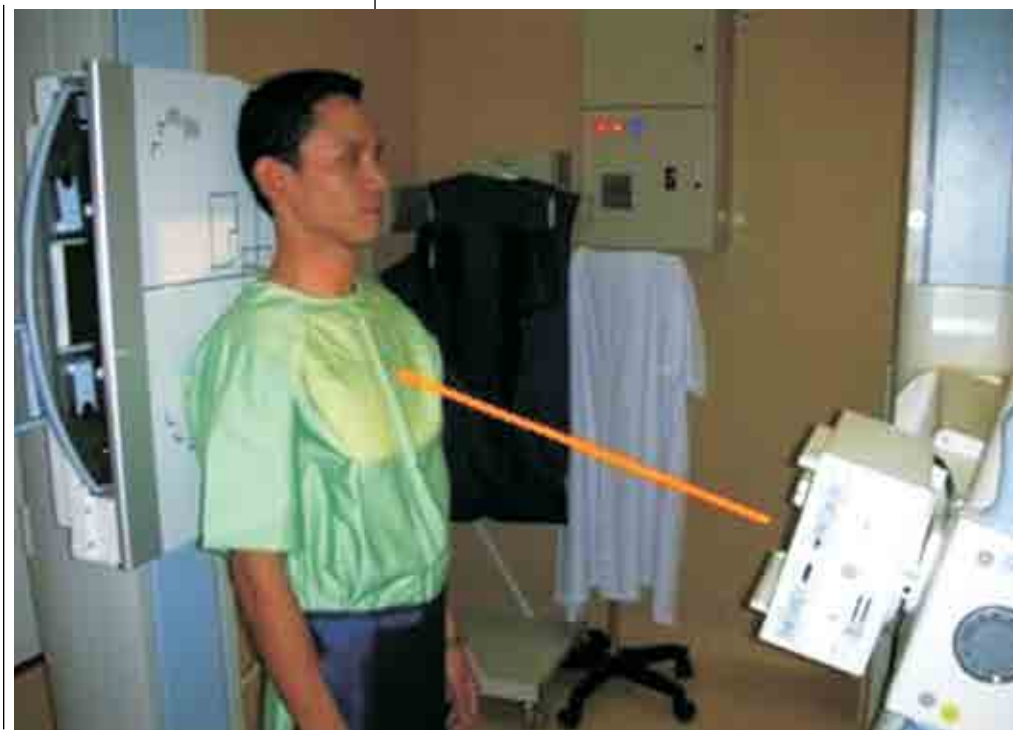

Figure 2 – Principle behind the lordotic CXR (Source: http://nexradiology.blogspot.ca)

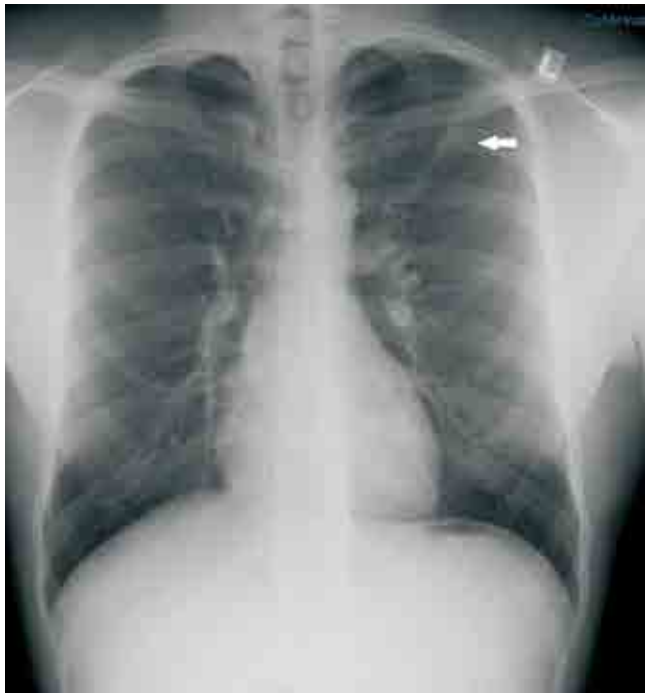

Figure 3a – In this patient, a lesion was suspected (arrow), but hidden by the left 2nd rib

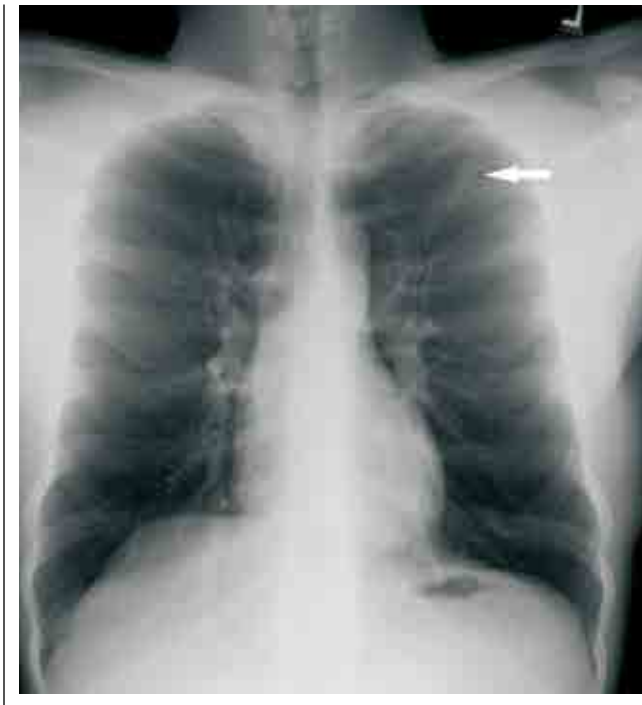

Figure 3b – Lordotic film on the patient in Figure 3a showed cavitary lesion (arrow) and culture grew TB

changes. In **Figure 4,** a routine screening film showed minor densities in the LUL (left upper lobe). Sputum induction was done and the sample grew active TB. Sputum cultures are important whenever there is parenchymal disease. If the patient is not coughing, spontaneous sputum is of little value. Sputum induction is very helpful in getting a sample.

LOCATION OF DISEASE

TB prefers the apices of the lung, but that also applies to the lower lobes apices, i.e., the superior segments. **Figure 5** illustrates a case of cavitary TB affecting the superior segment of the RLL (right upper lobe).

EXTENSIVE DISEASE

Figure 6 shows that TB can be very extensive and, in this case, destroying the entire left lung, and also involving the right apex. Note also the lack of soft tissues under the skin of the chest wall, indicating extreme cachexia. The patient subsequently died of his disease. Extensive, cavitary TB is, sadly, common in India and late diagnosis and treatment is a major reason for this.

CULTURE-NEGATIVE TB

In cases where the CXR and clinical history is very suggestive of TB but smears are negative, treatment can be started pending culture results. Negative cultures but x-ray improvement on therapy is suggestive of culture-negative TB. Remember that even in the context of good sputum collection with induction, three sputum cultures have a sensitivity of 90%, which means you will miss 10% of cases of active TB. In the following case (**Figure 7a**) the patient was from a TB endemic country, had a positive Mantoux skin test and a one month history of cough.

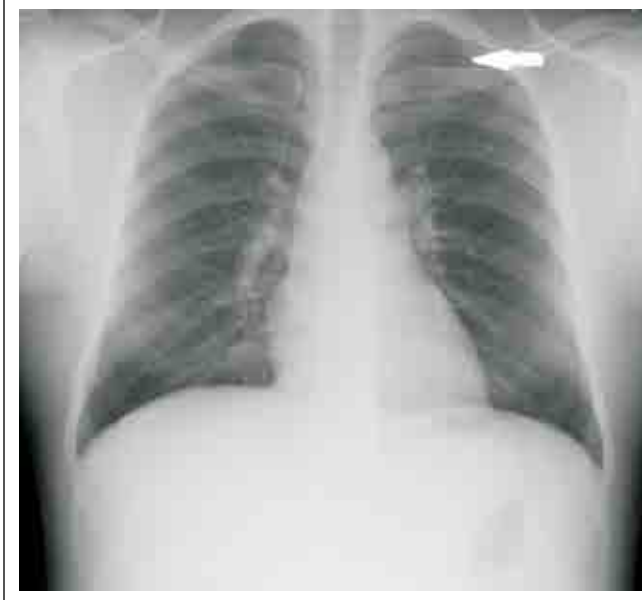

Figure 4 – Minimal TB with minor densities in the LUL. Induced sputum grew TB on culture

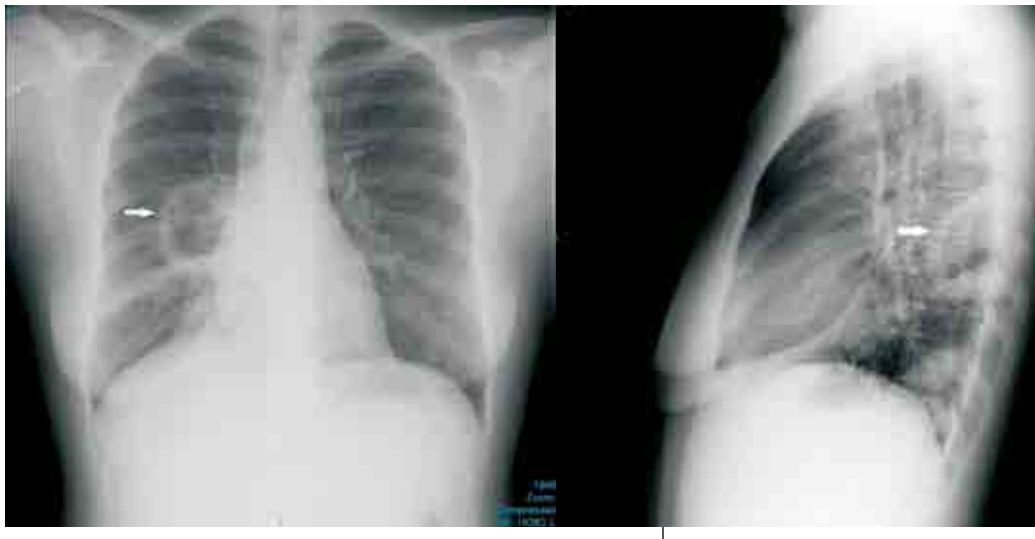

Figure 5 – Cavitary TB affecting the superior segment of the RLL (arrow points to a thick walled cavity)

Three sputum smears and cultures were done and the patient was started on TB drugs. All cultures were negative but a CXR one month later showed resolution of the infiltrates (**Figure 7b**)

PLEURAL TB

Pleural effusion is a common manifestation of TB. It can be a consequence of both primary and reinfection TB. It often resolves with proper antibiotic therapy, but can leave residual pleural thickening and even calcification. **Figure 8a** is a case of a young patient from a TB endemic country who presented with a one month history of fever and left sided chest pain. Thoracentesis revealed an exudate with low glucose, low pH and a high lymphocyte count. A presumptive diagnosis of TB was made and TB medications were started. The fluid was smear negative (as is often the case in pleural TB) but the cultures grew MTB. The subsequent CXR taken six months later (**Figure 8b**) shows reabsorption of the fluid with residual pleural thickening.

In another case (**Figure 8c**), extensive pleural calcification has developed. This often occurred in the pre-antibiotic era, when recurrent pneumothoraces were induced in the hope of reducing the size of the

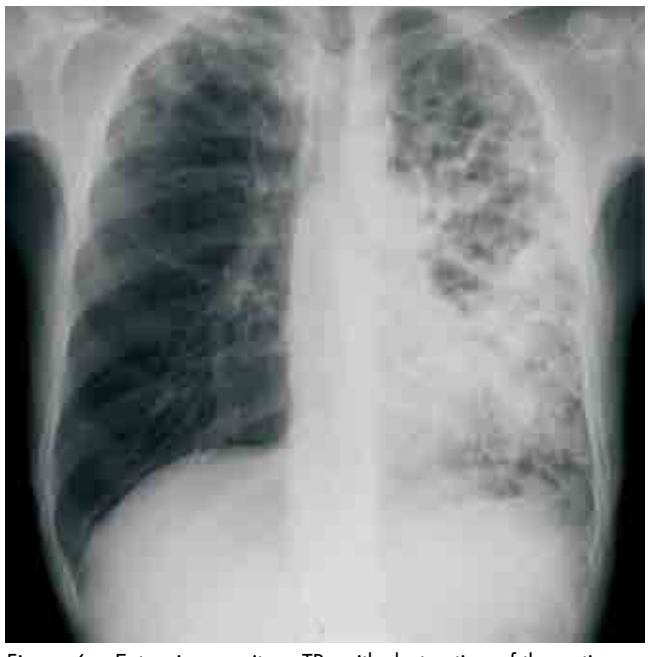

Figure 6 – Extensive, cavitary TB, with destruction of the entire left lung

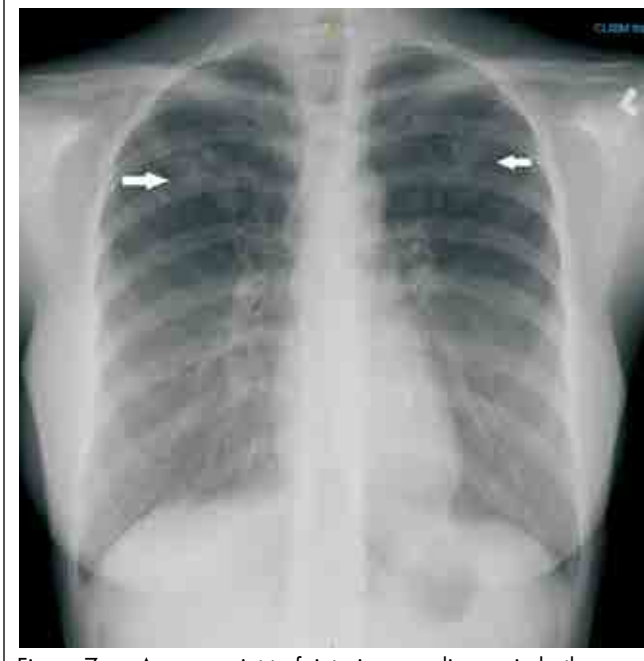

Figure 7a – Arrows point to faint airspace disease in both upper lobes

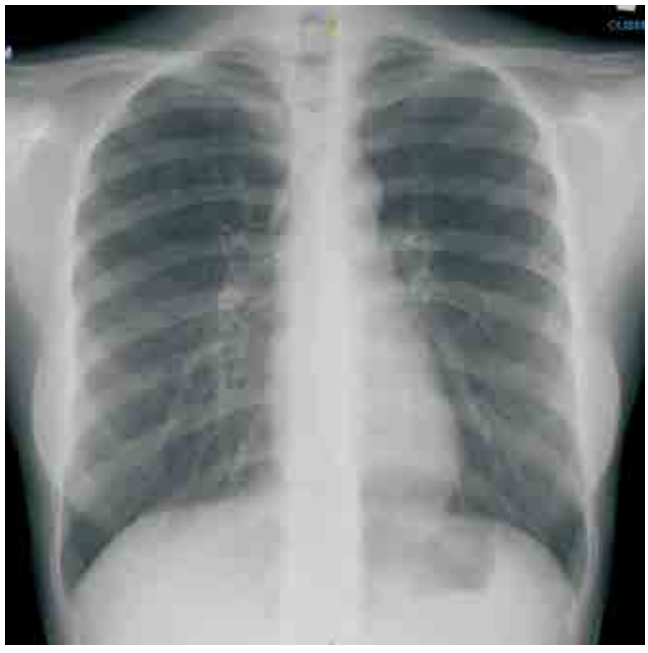

Figure 7b – A CXR shows resolution of the infiltrates after TB therapy

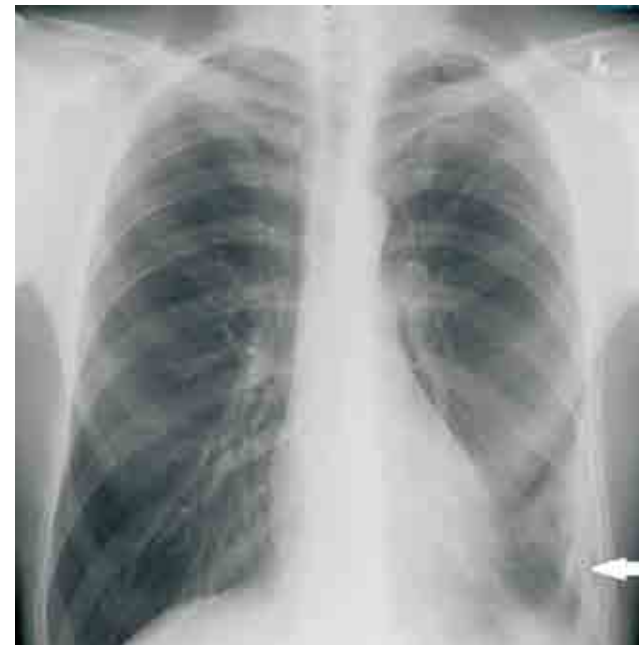

Figure 8b – On this CXR, the arrow points to pleural thickening (earlier CXR shown in Figure 8a)

cavity. These pneumothoraces often resulted in repeated infections of the pleural space and subsequent calcification.

MILIARY TB

Miliary TB is a result of hematogeous dissemination of the mycobacteria. It presents with a micronodular (1-4 mm in size) pattern distributed diffusely though out both lungs (**Figure 9**). It can arise as a result of progressive primary infection or via reactivation.

PRIMARY TB

Primary TB results from the failure of the host to suppress the initial infection. It present as pneumonia in

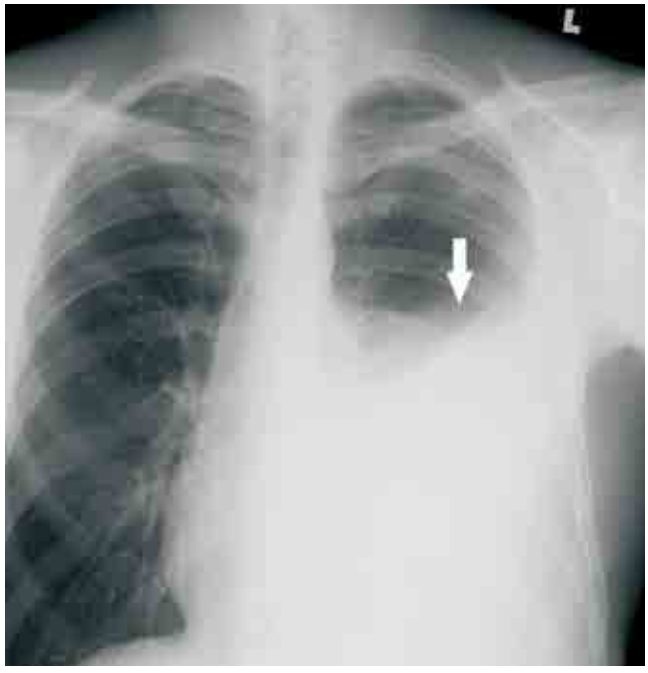

Figure 8a – This CXR shows a large left pleural effusion

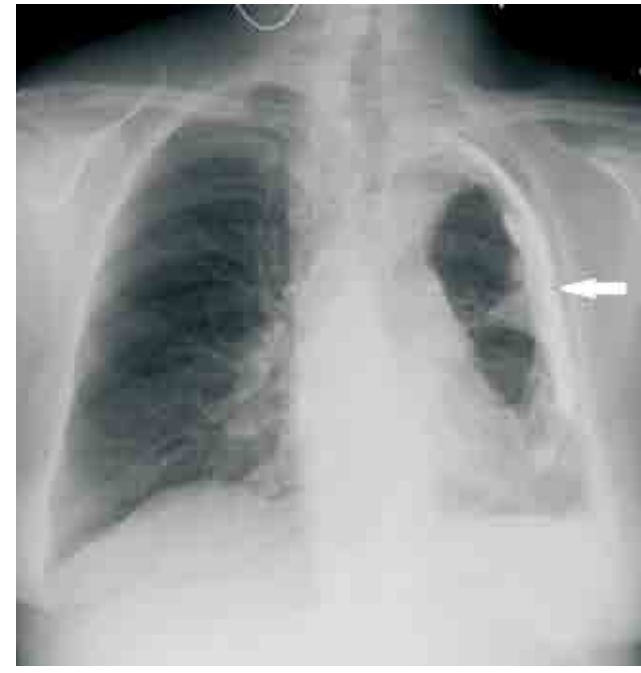

Figure 8c – This CXR shows extensive left pleural calcification

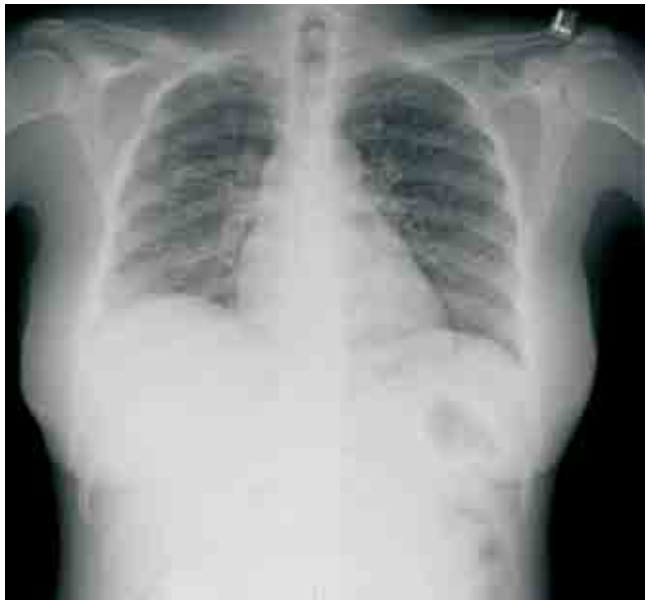

Figure 9 – Miliary TB, with diffuse micronodules distributed though out both lungs

the lower lobes, lingula or right middle lobe (RML) as opposed to reactivation TB, which tends to favor the apical regions. It can also cause pleural effusion or miliary TB. **Figure 10** shows the CXR of a TB contact who had a 2 week history of cough and fever. Sputum smears and culture were positive.

Another case finding in a TB contact investigation showed a RLL cavity that was smear positive (**Figure 11**).

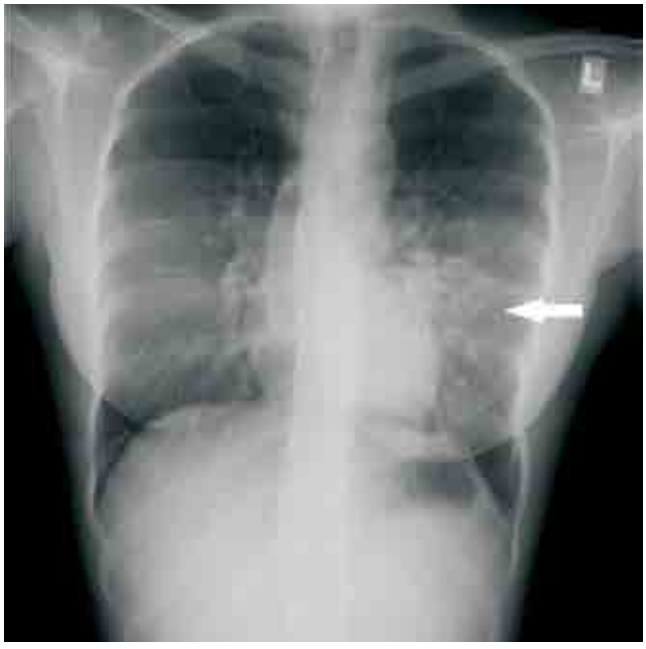

Figure 10 – Infiltrate in lingula in a case of primary TB

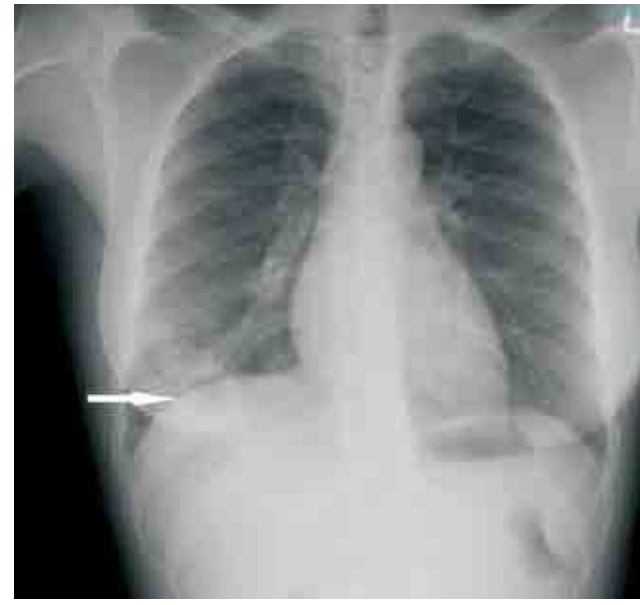

Figure 11 – Arrow points to cavity in the RLL

TB ADENOPATHY

TB adenopathy is a common presentation of extrapulmonary TB. It is often a manifestation of primary TB. It can affect both mediastinal and hilar lymph nodes (**Figure 12**).

TB MAY MIMIC OTHER DISEASES

The CXR below in **Figure 13** is of a 55 year old woman, 30 pack-year smoker, who presented with a one

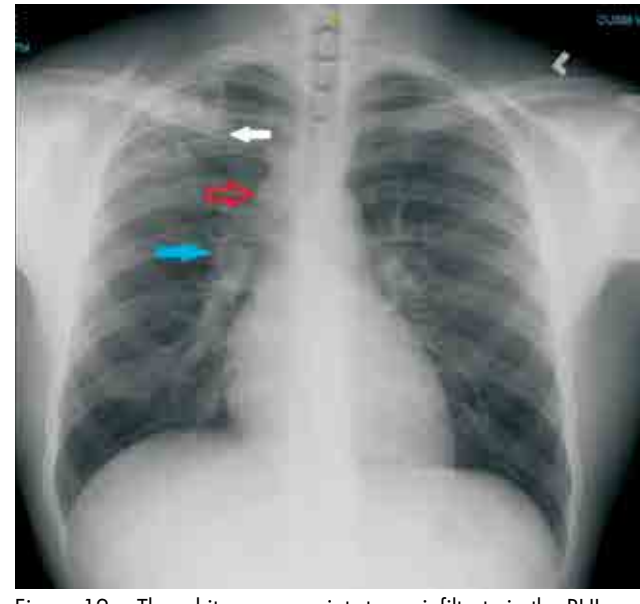

Figure 12 – The white arrow points to an infiltrate in the RUL. The red arrow shows paratracheal adenopathy. The blue arrow points to a right hilar node

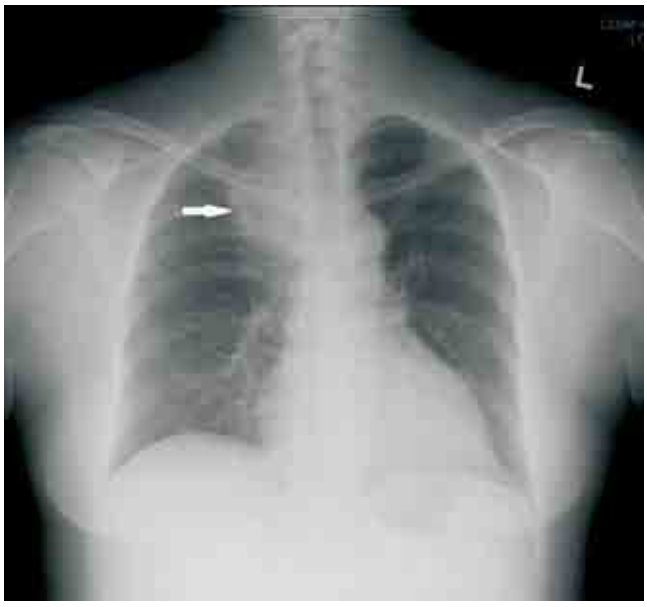

Figure 13 – Mass abutting the mediastinum in the RUL. While cancer was suspected, cultures grew MTB

month history of cough and weight loss. There was no fever. The CXR shows a mass abutting the mediastinum in the RUL. Cancer was suspected and a brochoscopy was done. Pathology revealed necrotizing granulomas and cultures were positive for TB.

The next case is a 65 year old man, 40 pack-year smoker who had a routine CXR which showed a cavitary nodule in the RUL (**Figure 14**). He was asymptomatic. A CXR done a year previously was normal. Biopsies

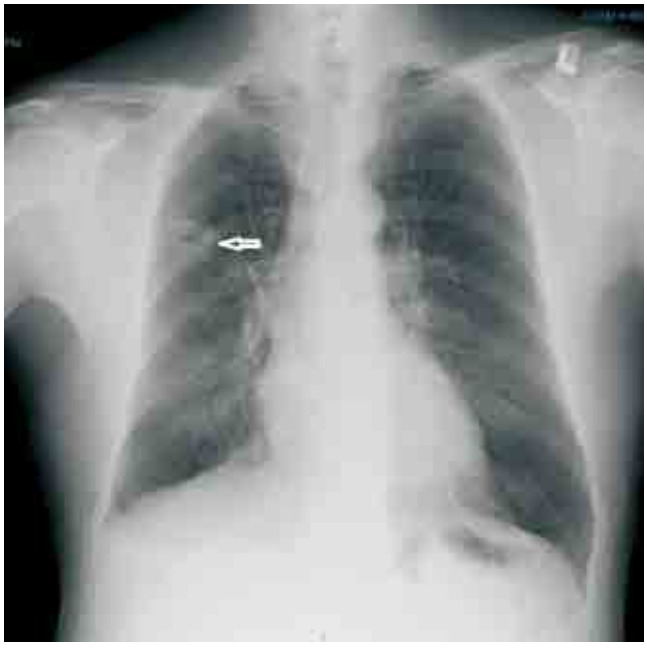

Figure 14 – Arrow points to a cavitary nodule in the RUL

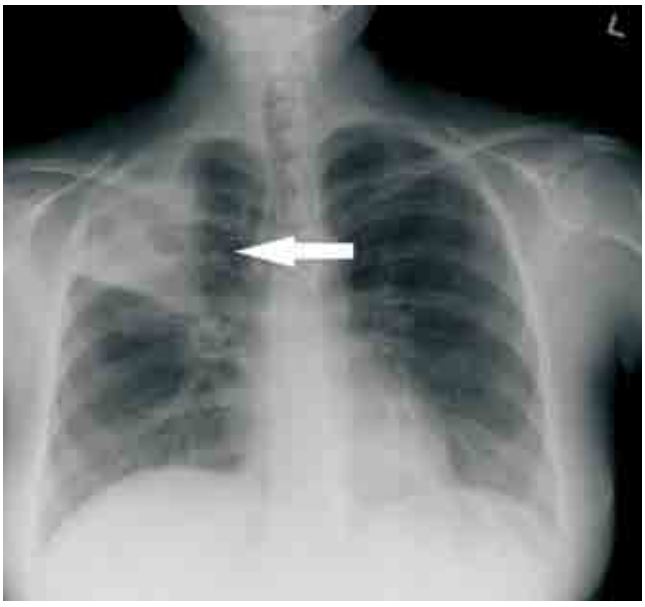

Figure 15a – CXR shows a consolidation in the RUL

were negative. Lung cancer was suspected and a thoracotomy was done. The resected lobe showed TB.

DISEASES WHICH MAY MIMIC TB

Figure 15a is CXR of a 40 year old woman who comes from a TB endemic country. The CXR shows a consolidation in the RUL. There was a one week history of fever, chills and cough with purulent sputum. Due to the short history, an acute bacterial pneumonia was

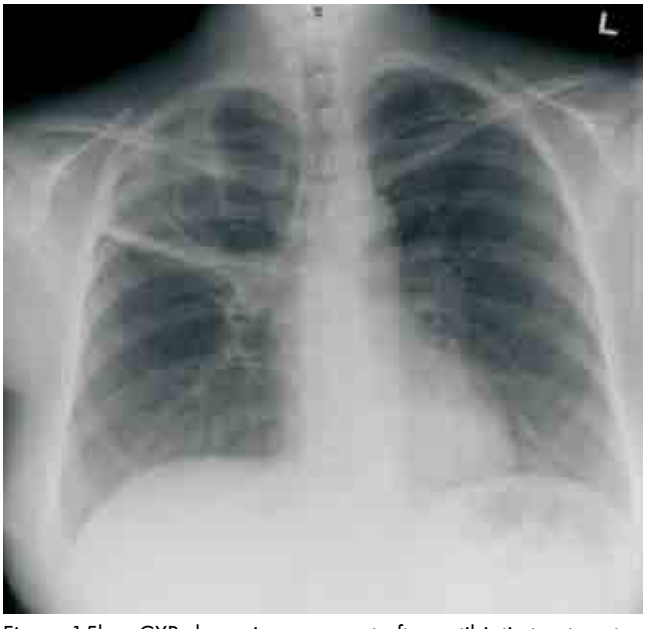

Figure 15b – CXR shows improvement after antibiotic treatment with azithromycin

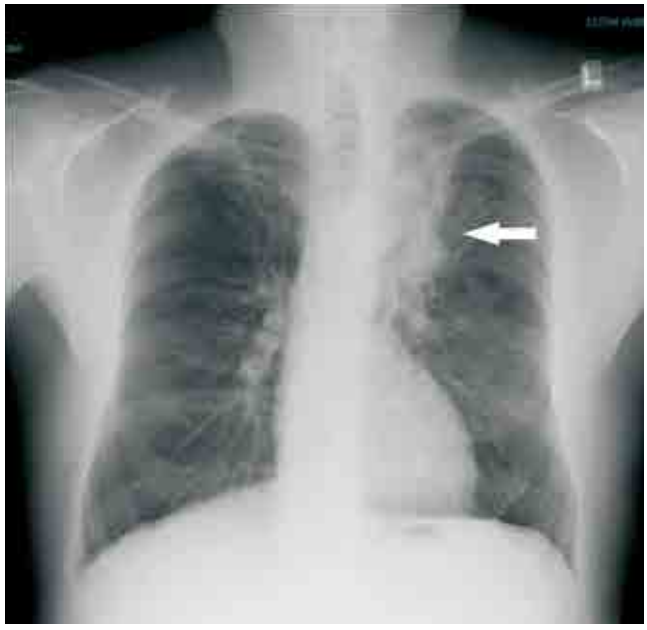

Figure 16a – CXR shows a dense infiltrate in the LUL.

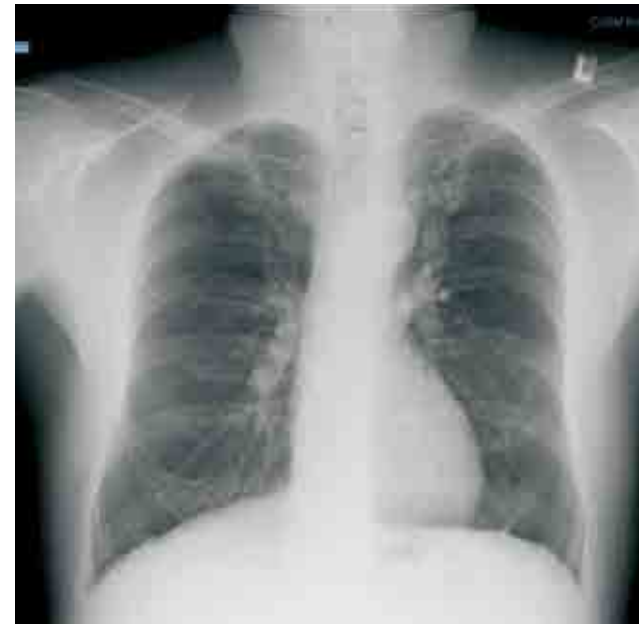

Figure 16b – CXR shows resolution

suspected and treatment with azithromycin was started. She promptly became afebrile and the CXR improved within a week. (**Figure 15b**).

Upper lobe pneumonias in patients from endemic countries should not be treated with fluoroquinolones because if it is TB, it will respond (temporarily) to this class of antibiotics, and make it much harder to diagnose TB later.[2]

The next case is a 56 year old man with extensive travel to Asia. He had a 4 month history of recurrent cough and fever and wheezing. He had received many courses of antibiotics, with temporary improvement. He was known to have asthma. The CXR (**Figure 16a**)

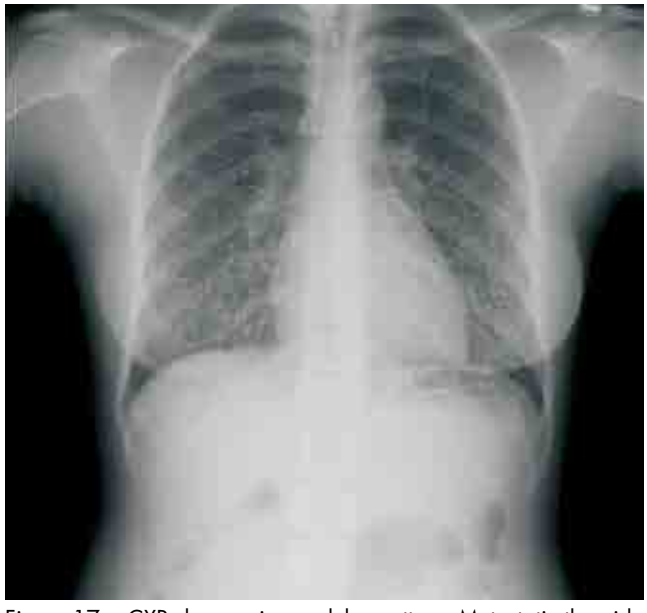

Figure 17 – CXR shows micronodular pattern. Metastatic thyroid carcinoma was the final diagnosis

CLINICAL HIGHLIGHTS

- ❑ Radiology is a useful tool for diagnosis and monitoring of TB, but it should not be used alone. Microbiological diagnosis is critical to confirm TB.
- ❑ There are many radiologic manifestations of TB. TB can affect lung parenchyma, interstitium, pleura, pericardium, lymph nodes and bones.
- ❑ There are many diseases which can mimic TB, and TB can look like other diseases, so it is neither specific nor sensitive.
- ❑ HIV infection can alter the radiological appearance of TB and must be kept in mind while interpreting x-rays.
- ❑ Although one can suspect TB from the radiologic and clinical picture, confirmation of disease depends on sputum smear, PCR and culture.
- ❑ Treatment of TB purely on the basis of x-rays can result in significant over-treatment with adverse consequences for patients.
- ❑ Therefore, all persons with chest radiographic findings suggestive of TB should have sputum specimens submitted for microbiological examination.

showed a dense infiltrate in the LUL. Sputum AFB was negative but because of the history of asthma allergic bronchopulmonary aspergillosis was suspected. Serum IgE was 9,000 and aspergillus precipitins were positive. He was given a course of prednisone, with clinical and radiologic resolution (**Figure 16b**).

Figure 17 is a CXR of a 17 year old girl from Burundi. She had a 4 month history of intermittent fever and cough. Her CXR shows a micronodular pattern. Because of her country of origin and her symptoms, military TB was suspected and she was started on TB therapy. There was no improvement after 2 weeks and so a transbronchial biopsy was done, which revealed metastatic thyroid carcinoma. The fever was due to malaria.

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CIS CME–Questions

Interpretation of Chest X-rays in Tuberculosis

Questions

1. **Which of these statements is NOT true about chest radiology for TB diagnosis?**
   a. Chest x-rays are highly specific for TB
   b. All persons with radiographic abnormalities suggestive of TB should have sputum specimens submitted for microbiological examination
   c. Treatment of TB purely on the basis of x-rays can result in significant over-treatment
   d. HIV infection can alter the radiological appearance of TB

2. **The commonest radiologic finding in TB is:**
   a. Pleural effusion
   b. Upper lobe consolidation with or without cavities
   c. Pericardial effusion
   d. Lung nodule

3. **TB cannot occur in the:**
   a. Upper lobes
   b. Lower lobes
   c. Lingula
   d. RML
   e. None of the above

4. **A patient presents with a 10 day history of high fever, cough and purulent sputum. A CXR shows a dense consolidation in the RUL. The next step is:**
   a. Obtain sputum specimens for AFB and start TB treatment
   b. Start a course of moxifloxacin
   c. Obtain sputum specimens for AFB and culture/sensitivity examination and start azithromycin
   d. Refer the patient to a TB hospital

5. **A 55 year old 40 pack year smoker consults with you for a 2 month history of cough and blood tinged sputum (no fever). He reports that his sister had TB 10 years ago. The CXR shows a cavitary mass in the RUL. What is the next step?**
   a. Obtain sputum AFB
   b. Send sputum for cytology
   c. Send patient for a bronchoscopy
   d. Start treatment with an antibiotic

(See answers on the next page)

CIS CME–Answers

Interpretation of Chest X-rays in Tuberculosis

Questions on the previous page

Answers

1. **The correct answer is (a).** Chest x-rays are not specific for TB. Many lung infections and conditions can cause radiological abnormalities. This is why all persons with radiographic abnormalities suggestive of TB should have sputum specimens submitted for microbiological examination.[1] Only microbiological examination can confirm the diagnosis of TB.[2]

2. **The correct answer is (b).** Although TB can cause any of the radiologic findings listed, upper lobe disease with or without cavitation is the most common.[3,4]

3. **The correct answer is (e).** Although TB most commonly occurs in the upper lobes it can occur in any part of the lung.

4. **The answer is (c).** CXR's must be interpreted in the clinical context. An acute presentation suggests acute bacterial infection. Sputum specimens should be obtained before starting conventional antibiotics. Fluoroquinolones should be avoided if TB is at all suspected as they will result in temporary improvement because TB is sensitive to this class of drugs, leading to delay in diagnosis.

5. **The answer is (c).** Although TB must be suspected in anyone with an upper lobe cavitary mass, in a heavy smoker with a 2 month history of cough and bloody sputum, in the absence of infectious symptoms, lung cancer must be suspected. A bronchoscopy can obtain specimens for AFB but at the same time, can make the diagnosis of cancer.

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Let's Talk TB

A Series on Tuberculosis, A Disease That Affects Over 2 Million Indians Every Year

Improving Access to Affordable and Quality TB Tests in India

Madhukar Pai, MD, PhD—Author and Series Editor

Abstract

This article describes the Initiative for Promoting Affordable, Quality TB tests (IPAQT; www.ipaqt.org), a coalition of private laboratories in India, supported by industry and non-profit groups, that has made several WHO-endorsed TB tests available at more affordable prices to patients in the private sector. General practitioner who manage TB should avoid inaccurate blood-based tests and use WHO-endorsed sputum tests for TB, including LED fluorescence smear microscopy, liquid cultures, line probe assays, and automated, cartridge-based molecular tests (i.e., Xpert MTB/RIF). These tests are validated and backed by strong evidence and WHO policy recommendations. Thanks to IPAQT, their prices have been reduced considerably in the Indian private sector.

Key words: tuberculosis, diagnosis, India, private sector

INTRODUCTION

Tuberculosis (TB) remains one of India's biggest health problems. Every year, India reports over 2 million TB cases. With the emergence of severe forms of drug-resistant TB, and concerns about TB drug shortages, there is much work to be done to control the epidemic.[1]

The Revised National TB Control Programme (RNTCP) has made good progress by providing basic TB diagnosis and treatment free of cost to all patients in the public sector. Recently, the RNTCP announced "*universal access to quality TB diagnosis and treatment for all TB patients in the community*"as its new goal for the next five-year plan.[2] This is a worthy goal, but any plan to reach all TB patients in India will need to include India's dominant private sector.

Why is the private health sector critical? In general, more than 80% of India's health care is delivered through the private sector. Most poor people who develop a cough first seek care in the informal private sector (chemists and unqualified practitioners), then from qualified practitioners.[3] Ultimately, about 50% of them end up in the public sector where they receive free treatment.[4] This pathway to curative care can take from weeks to months, during which patients continue to transmit infection to others. This delay, coupled with the high cost of care in private sector, drives many poor families into debt. And yet, for all the money spent, patients frequently undergo inaccurate TB tests and inappropriate TB drug treatment.[5,6] Consequently, promptly getting patients the right test in the private sector is a critical first step for interrupting transmission and reducing the risk of drug resistance.

Unfortunately, TB testing practices in the private sector are completely different from those in the public sector. A majority (more than 90%) of TB tests done by RNTCP are sputum smears. Diagnosis in the private sector is characterized by overuse of unreliable blood tests, low availability and high cost of reliable quality-assured diagnostics tools, preference of blood as a sample, inability of the providers to separate the good from the bad tests, and the commercial incentives that inflate cost to the patients.[5,7]

Worldwide, sputum is the most important sample for diagnosis of lung TB and every guideline recommends the use of sputum-based

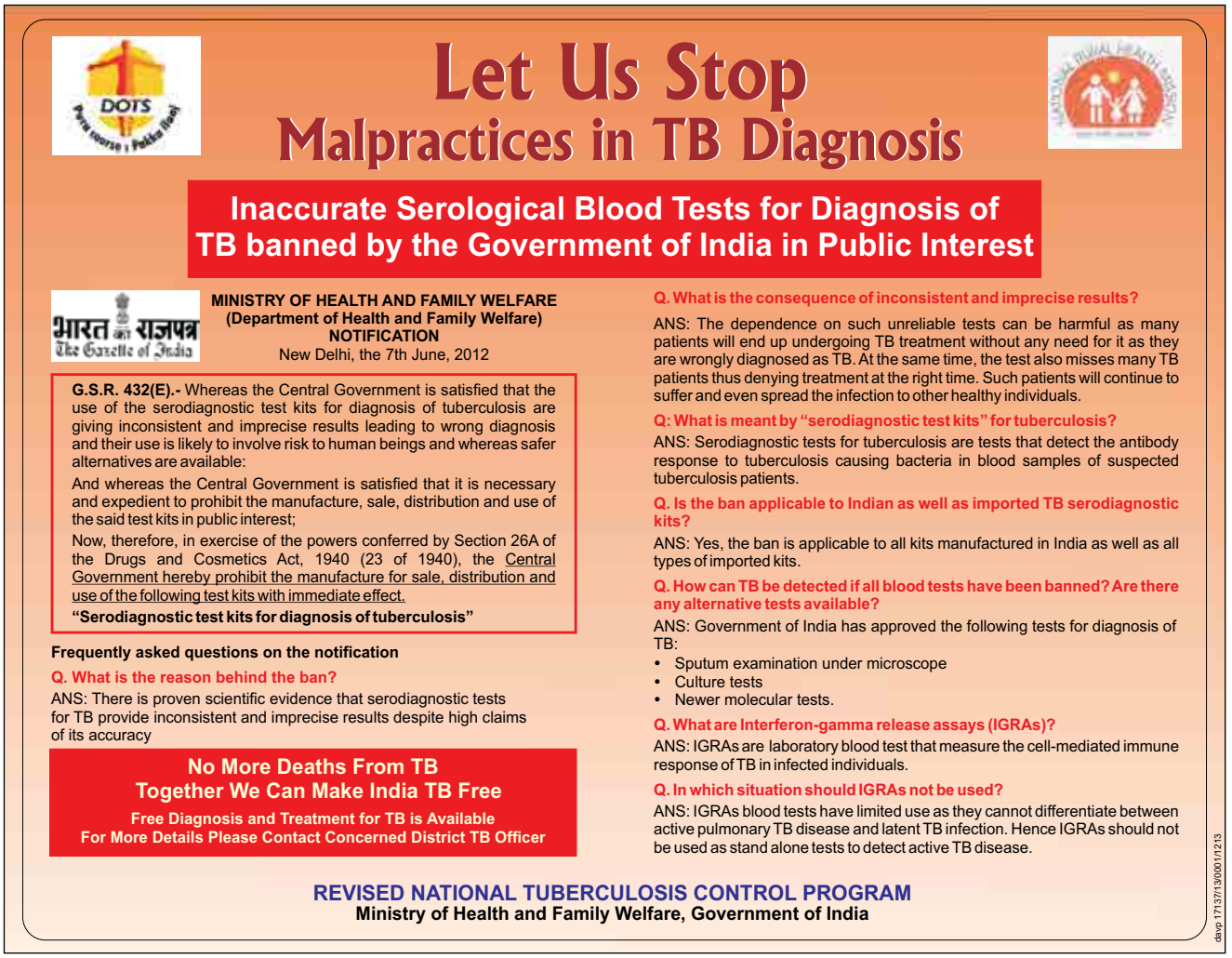

Figure 1 – Advertisement on the ban on TB serological tests, published by the Ministry of Health and Family Welfare in leading Indian newspapers in 2012. (open access at http://www.davp.nic.in/WriteReadData/ADS/eng_17137_1_1213c.pdf)

tests. But, for several reasons, including poor regulation and financial incentives, blood is the most popular sample in the Indian private sector.[5] Blood-based antibody tests are not accurate and discouraged by the World Health Organization (WHO).[8,9]

India's diagnostic landscape changed in June of 2012 when the Government of India, acting on the 2011 WHO policy against serological tests, banned the use, import, sale and manufacture of antibody-based blood tests for TB, and discouraged the use of interferon-gamma release assays (IGRAs) like "TB Gold" and "TB Platinum" for active TB (**Figure 1**).

Blood-based antibody tests have no clinical role in TB diagnosis and not recommended by any agency. There are acceptable blood tests (such as QuantiFERON-TB Gold, marketed in India as "TB Gold") for latent TB infection (which is treated with 6 – 9 months of isoniazid, to prevent progression from latent infection to active disease). These latent TB tests, however, are not recommended for active TB diagnosis by the WHO.[10] Use of IGRAs for active TB will result in unacceptably high rates of false-positive results because IGRAs, like the Mantoux tuberculin skin test, cannot separate latent TB infection from active TB disease, and a large proportion of the Indian population is latently infected.[11]

Since the serology ban created a void in the market, it is important to address this gap and make sure that WHO-endorsed, sputum-based TB tests replace the inappropriate blood tests in the private sector. There are 4 accepted sputum tests that are recommended by the WHO and these are also used by the RNTCP. These are sputum smears, Xpert MTB/RIF, line probe assay and liquid cultures.

Although not highly sensitive, smear microscopy test is still very useful (and cheap) because it can rapidly iden-

CLINICAL HIGHLIGHTS

- ❑ Tuberculosis (TB) remains one of India's biggest health problems. Every year, India reports over 2 million TB cases.
- ❑ Recently, the RNCTCP announced "Universal access to quality TB diagnosis and treatment for all TB patients in the community".
- ❑ Unfortunately, TB testing practices in the private sector are completely different from those in the public sector. A majority (more than 90%) of TB tests done by RNTCP are sputum smears; while blood is the most popular sample in the Indian private sector.
- ❑ Blood-based antibody tests have no clinical role in TB diagnosis and not recommended by any agency.
- ❑ There are 4 accepted sputum tests that are recommended by the WHO, and are also used by the RNTCP. These are sputum smears, Xpert MTB/RIF, line probe assay and liquid cultures.
- ❑ A new initiative (IPAQT) was launched in March 2013 to improve the affordability of WHO-endorsed TB tests.
- ❑ The IPAQT (Initiative for Promoting Affordable, Quality TB tests) is a coalition of private labs in India, supported by industry and non-profit groups (e.g., Clinton Health Access Initiative), that has made WHO-endorsed tests available at affordable prices to patients in the private sector.
- ❑ IPAQT aims to facilitate the delivery of WHO-endorsed tests to the TB patient at affordable prices, and promote the use of WHO-endorsed TB tests by building awareness about these new, validated/endorsed tests among health providers, laboratories and patients.
- ❑ Due to IPAQT, the cost of Xpert MTB/RIF is now reduced to Rs 2000 (maximum price labs can charge patients). The line probe assay (Hain Genotype MTBDRplus Version 2) is now available at Rs 1600. The MGIT liquid culture by BD is available for Rs 900 for detection.
- ❑ TB cases diagnosed via IPAQT member labs will be notified to the RNTCP for linkages to free TB drugs, where necessary.
- ❑ Any Indian laboratory can join IPAQT, provided they are accredited by a recognized agency (e.g., National Accreditation Board for Testing and Calibration Laboratories [NABL]), and agree to abide by the guiding principles of IPAQT.

tify the most infectious patients, and it is simple enough to be done in peripheral laboratories. Microscopy is under-used in the private sector, and this needs to change.

Recently, the WHO endorsed a new, rapid, automated, 2-hour molecular test called Xpert MTB/RIF, based on the GeneXpert platform (Cepheid Inc, USA), which can diagnose TB with great accuracy and can also detect those with drug-resistance.[12] A recent Cochrane review has shown that the Xpert MTB/RIF test has 88% sensitivity and 98% specificity when compared to culture.[13] Xpert MTB/RIF can detect rifampicin resistance with a sensitivity of 94% and specificity of 98%.[13] Data from many countries, including India, clearly show substantially better performance of the Xpert MTB/RIF test over conventional smear microscopy.[13] Emerging data also suggest that Xpert MTB/RIF has value for extrapulmonary TB (EPTB), especially TB lymphadenitis and TB meningitis. A WHO policy on the use of Xpert MTB/RIF for EPTB and childhood TB was published in 2013, and WHO endorsed Xpert for childhood TB, and some forms of EPTB.

Another WHO-endorsed rapid molecular test, the line probe assay (e.g., Genotype MTBDRplus by Hain Lifescience, Germany) can also detect resistance to INH and rifampicin with high accuracy, and allow for rapid initiation of MDR-TB treatment, while waiting for liquid culture and DST.[14] Lastly, liquid cultures (e.g., MGIT by BD, USA, and BacT/Alert by BioMerieux, France) are considered the gold standard for TB diagnosis and the only technology that can detect resistance to all major TB drugs. Liquid cultures are also very useful for smear-negative TB and EPTB.

If private physicians and laboratories replace suboptimal tests with the above sputum tests, this should greatly help improve the accuracy of TB diagnosis for patients in the country. The challenge is that good tests like GeneXpert, line probe assay and liquid culture are very expensive in the private sector. For example, the GeneXpert test can cost the patient as much as Rs. 3500 or higher in private laboratories. This is because WHO-endorsed tests are available at specially negotiated low prices only to the public sector, and import duties also add to the costs. In addition, financial incentives and laboratory margins further inflate the costs to make them virtually unaffordable to the average private sector patient.

This has now changed, thanks to a new initiative launched in March 2013, to improve the affordability of WHO-endorsed TB tests. Initiative for Promoting Affordable, Quality TB tests (IPAQT; www.ipaqt.org) is a coalition of private labs in India, supported by industry and non-profit groups (e.g., Clinton Health Access Initiative), that has made WHO-endorsed tests available at affordable prices to patients in the private sector (**Figure 2**).[15]

(Continued on page 41)

IPAQT

INITIATIVE FOR PROMOTING AFFORDABLE AND QUALITY TB TESTS | www. ipaqt.org




EARLY AND ACCURATE DIAGNOSIS, FOLLOWED BY CORRECT TREATMENT, IS THE SOLUTION TO

TUBERCULOSIS

A DISEASE THAT EVEN TODAY,

KILLS ABOUT 1000 INDIANS EVERY DAY

THE NEED

TB affects 2 million people annually in India, and each undiagnosed and wrongly diagnosed case spreads the disease in their family and their community.

Approximately 4% of new TB patients have Multi-drug Resistant (MDR) strains of TB; among patients who had been treated for TB before, about 20% have MDR-TB.

While blood-based antibody tests have been popular in the private sector, these tests are inaccurate and banned by the Government of India. Blood-based tests like TB Gold and TB Platinum are meant for latent TB infection, not active TB.

There is a need to introduce affordable and accurate tests - i.e. those endorsed by the World Health Organization (WHO) and the Revised National TB Control Programme (RNTCP).

WHAT IT MEANS FOR YOUR PRACTICE

For the first time in India, via IPAQT, these WHO endorsed tests are being offered at substantially reduced prices. You can now get your patients tested for TB and MDR-TB and get fast results through molecular tests with high accuracy, offered by a network of quality-assured laboratories.

TO FIND A LAB NEAR YOU THAT IS A PART OF IPAQT AND FOR MORE INFORMATION ON THE TESTS PLEASE VISIT **WWW. IPAQT.ORG**

For updated information on IPAQT, please see brochure at the end of this booklet.

ABOUT IPAQT

IPAQT is an initiative of non-profit stakeholders and over 170 private labs/hospitals (approximately 10,000 collection centers) with a pan-India presence that have come together to provide WHO approved tests for TB at or below the following the patient prices

- **XPERT MTB/RIF TEST - Rs. 2200**
- **Genotype MTBDRplus TEST - Rs. 1800**
- **BACTEC MGIT LIQUID CULTURE - Rs. 900 for TB detection**
- **BacT/ALERT 3D liquid culture - Rs. 900 for TB detection**

(go to www.ipaqt.org for latest pricing information)

These 3 tests offer accuracy and speed are backed by strong evidence and WHO policy endorsements (www.who.int/tb/laboratory/policy_statements/en)

The Xpert MTB/RIF test (GeneXpert; Cepheid Inc.) can detect TB as well as Rifampicin resistance with high accuracy (about 90% sensitivity and 98% specificity) within hours.

The Genotype MTBDRplus (Hain Lifescience) assay can detect MDR-TB (INH and Rifampicin resistance) with high accuracy (about 98% sensitivity and 99% specificity for Rifampicin)

Liquid cultures are considered the gold standard for TB and offer the highest accuracy, with about 2 week turnaround.

Figure 2 – Flyer on the IPAQT initiative (www.ipaqt.org)

IPAQT aims to facilitate the delivery of WHO-endorsed tests to the TB patient at affordable prices, and promote the use of WHO-endorsed TB tests by building awareness about these new, validated/endorsed tests among health providers, laboratories and patients. Several private laboratories in India have agreed that in exchange for not exceeding negotiated, ceiling prices to patients, notifying the government of the cases diagnosed, promoting the use of these tests and participating in external quality assurance (EQA) they would get reagents at significantly reduced prices. In exchange for offering lower prices, the manufacturers and distributors would receive greater and more predictable volumes from the previously untapped private market.

The business model of IPAQT is based on a comparison of high margin low volume (premium) versus lower margin high volume (mass-market) pricing models. Thanks to IPAQT, the cost of Xpert MTB/RIF is now reduced to Rs 2200 (maximum price labs can charge patients). The line probe assay (Hain Genotype MTBDRplus Version 2) is now available at Rs 1800. The MGIT liquid culture by BD is available for Rs 900 for detection. These prices are approximately 30-50% less than the private market prices before IPAQT was launched, and the prices are comparable to the banned TB ELISA test for three antibodies. Thus, for the money patients were paying for inaccurate tests, they can now get WHO-endorsed, high-quality tests.

TB cases diagnosed via IPAQT member labs will be notified to the RNTCP for linkages to free TB drugs, where necessary. Any Indian laboratory can join IPAQT, provided they are accredited by a recognized agency (e.g., National Accreditation Board for Testing and Calibration Laboratories [NABL]), and agree to abide by the guiding principles of IPAQT. Laboratories that join IPAQT must agree to stop doing TB serology and avoid promoting tests (e.g., IGRAs) that are discouraged by the RNTCP.

Since its launch in March 2013, the IPAQT initiative has already achieved a pan-India presence – with over 170 labs, which encompasse over 5000 franchisee labs and collection centers committed to providing these tests at affordable prices. The number of labs is expected to increase significantly in the months ahead. Thus, this initiative is expected to greatly increase affordability for private sector patients, and improve the quality of TB care in the country. In the long run, removal of import duties for all WHO-endorsed TB tests (under lifesaving drugs exemption) along with encouraging domestic development of high-quality TB tests will be critical to achieving the RNTCP goal of universal access.

CONFLICTS OF INTEREST

The author has no financial or industry conflicts. He serves on the Governing Council of the Initiative for Promoting Affordable, Quality TB tests (IPAQT; www.ipaqt.org).

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Let's Talk TB

A Series on Tuberculosis, A Disease That Affects Over 2 Million Indians Every Year

Treatment of Pulmonary Tuberculosis: What Every GP Should Know

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Abstract

Nearly 50% of patients with TB in India are treated in the private sector. GPs therefore share the responsibility of TB control in India, and play a major role in preventing the spread of the disease by curing patients and arresting transmission. Every GP will need to consider TB as a differential diagnosis in persons with cough lasting two weeks or more, or with abnormal findings on chest radiography. In such patients, TB must first be microbiologically confirmed, either using sputum smear microscopy, Xpert MTB/RIF (i.e., GeneXpert), or liquid cultures. Once TB is confirmed, the next step is to begin the correct anti-tuberculosis therapy (ATT) regimen, as recommended by Standards for TB Care in India (STCI) and the International Standards for TB Care (ISTC). All patients who have not been treated previously and do not have other risk factors for drug resistance should receive a WHO-approved first-line treatment regimen for a total of 6 months. The initial phase should consist of two months of isoniazid, rifampicin, pyrazinamide and ethambutol. The continuation phase should consist of isoniazid and rifampicin given for 4 months (ethambutol can also be added to the continuation phase in areas with high levels of isoniazid resistance). Treatment can be given daily or as thrice-weekly intermittent dosing. Adherence to the full course of ATT is very important to ensure high cure rates and to prevent the emergence of drug-resistance. If patients have any risk factors for drug-resistance, or do not respond to standard ATT, they must be investigated for MDR-TB using drug-susceptibility tests (DST) like GeneXpert, line probe assays, and liquid cultures. MDR-TB requires long-term and specialized treatment. So, patients should be referred to chest specialists, either in the private sector, or in the public sector where free MDR treatment is available.

Key words: tuberculosis; treatment; drug regimen; adherence

INTRODUCTION

Previous articles in this series have covered various aspects of TB, including laboratory and radiological diagnosis.[1-4] Given the high incidence of TB in India, every GP in India must have a high index of suspicion for the disease in all patients with cough for more than two weeks, and in all patients with chest x-ray abnormalities.

If TB is suspected, it is important to order sputum tests that can microbiologically confirm TB.[1] Sputum TB tests that are widely used include smear microscopy, cultures, and molecular tests such as GeneXpert. These tests are all endorsed by the World Health Organization (WHO) and available at more affordable prices in the private sector, via the IPAQT initiative (www.ipaqt.org), which includes over 75 accredited private labs across India.[4,5]

It is important to note that pulmonary TB cannot be reliably detected by any blood test. Therefore, sputum is the most important sample to collect.[2] Chest x-rays are often very helpful, but they are not specific for TB, and must be followed by microbiological tests.[3]

Once TB is diagnosed, there are several key steps to ensure that patients have good outcomes:

- Assessment for multidrug-resistant TB (MDR-TB) risk factors

- Selection of correct first-line drug regimen, duration and dosage
- Ensuring treatment adherence
- Monitoring treatment success
- Management of adverse events
- Notification of TB cases
- Referral of patients with suspected MDR-TB

The effective treatment of tuberculosis has three aims:

- *The rapid reduction of bacillary load to ensure clinical improvement and to arrest transmission.* This is achieved through the use of potent bactericidal drugs such as isoniazid and rifampicin.
- *The prevention of the emergence of drug resistant strains.* The emergence of such strains is dependent on bacillary load and spontaneous mutations occurring in multiplying bacilli within the lungs. The concurrent use of multiple anti-tuberculous drugs is aimed at suppressing the growth of such mutants, and is an important component of an adequate regimen for treatment.
- *Prevention of relapse.* This is achieved through prolonged treatment, especially with a regimen that includes rifampicin, and monitoring of adherence to ensure elimination of any residual, persistent organisms, which are known to responsible for relapse.

STANDARDS FOR TB CARE

Two important standards for TB care were released in March 2014: the 3rd edition of the International Standards for TB Care (ISTC)[6], and the 1st edition of Standards for TB Care in India (STCI).[7] These standards establish the best practices for TB diagnosis, treatment and follow-up, and must be followed by all practitioners. Important recommendations from these standards are provided below.

ASSESSMENT FOR MDR-TB RISK FACTORS

Before TB treatment is started, practitioners must assess the patient for MDR-TB risk. According to the ISTC, 'an assessment of the likelihood of drug resistance, based on history of prior treatment, exposure to a possible source case having drug-resistant organisms, and the community prevalence of drug resistance (if known), should be undertaken for all patients. Drug susceptibility testing should be performed at the start of therapy for all patients at a risk of drug resistance. Patients who remain sputum smear-positive at completion of 3 months of treatment, patients in whom treatment has failed, and patients who have been lost to follow-up, or relapsed following one or more courses of treatment should always be assessed for drug resistance. For patients in whom drug resistance is considered to be likely an Xpert MTB/RIF (GeneXpert) test should be the initial diagnostic test. If rifampicin resistance is detected, liquid culture and testing for susceptibility to isoniazid, fluoroquinolones and second-line injectable drugs should be performed promptly.'[6]

SELECTION OF CORRECT FIRST-LINE DRUG REGIMEN

In India, several studies have shown widespread use of incorrect and irrational TB drug prescriptions, especially in the private sector.[8-10] Incorrect prescriptions can lead to emergence of drug-resistance and result in poor patient outcomes.[11,12] This underscores the importance of clinician education and adherence to standards.

According to the ISTC, 'all patients who have not been treated previously and do not have other risk factors for drug resistance should receive a WHO-approved first-line treatment regimen using quality assured drugs. The **initial phase** should consist of two months of isoniazid, rifampicin, pyrazinamide and ethambutol. The **continuation phase** should consist of isoniazid and rifampicin given for 4 months. The doses of antituberculosis drugs used should conform to WHO recommendations. Fixed dose combination drugs may provide a more convenient form of drug administration.'[6]

The STCI recommends that the continuation phase should consist of three drugs (isoniazid, rifampicin and ethambutol) given for at least four months.[7] This is because of the high levels of isoniazid resistance in India.

Evidence suggests that both daily and thrice-weekly intermittent drug regimens are acceptable for first-line TB therapy, provided mechanisms are put in place to ensure adherence. Intermittent drug therapy makes it easier to implement directly observed therapy (DOT), while daily treatment provides a great margin of safety. Dosages of drugs must be based on body weight and acceptable ranges are shown in **Table 1** (based on ISTC).[6]

Where possible, according to STCI and ISTC, fixed dose drug combinations (FDC) should be used because they reduce the number of pills taken daily, increase patient convenience and reduce the potential for medication errors.[6,7]

With respect to duration of therapy, 6 months is the standard for first-line therapy. The STCI recommends that the duration of the continuation phase can be extended by 3 – 6 months in special situations like bone and joint TB, spinal TB, and central nervous system involvement.[7]

ENSURING TREATMENT ADHERENCE

Since drug-sensitive TB requires at least 6 months of continuous therapy, ensuring adherence is a big challenge. Providing support for, and making every effort to ensure

Table 1 – Doses of first-line antituberculosis drugs in adults and children

Drug	Recommended dose in mg/kg body weight (range) Daily regimen			Three times weekly regimen		
Isoniazid	**Dose**	**Range**		**Dose**	**Range**	
Children	10	(7-15),	maximum 300 mg/day			
Adults	5	(4-6),	maximum 300 mg/day	10	(8-12),	maximum 900 mg/dose
Rifampicin						
Children	15	(10-20),	maximum 600 mg/day			
Adults	10	(8-12),	maximum 600 mg/day	10	(8-12),	maximum 600 mg/dose
Pyrazinamide						
Children	35	(30-40),	maximum 2000 mg/day			
Adults	25	(20-30),	maximum 2000 mg/day	35	(30-40),	maximum 3000 mg/dose
Ethambutol						
Children	20	(15-25),	maximum 1000 mg/day	30	(25-35),	maximum 2400 mg/dose
Adults	15	(15-20),	maximum 1600 mg/day			

Source: ISTC, 3rd edition (reference 6)

adherence should be considered to be part of the prescription for the treatment of TB. It is important to develop an approach that is tailored to each patient and one that involves an agreement between the GP and the patient.

Every TB patient should receive counseling at the start of TB treatment. They should be informed that they have a curable disease called TB, and that completion of the entire 6 month course is critically important to prevent poor outcomes.

Patients should also be informed about likely adverse drug events, and they should get a clear plan on when to come back for follow-up visits. Mobile phone reminders may help with improving adherence and follow-up visits. Patients also need to be advised about diet, return to work, smoking and alcohol cessation, and may need to be screened for comorbid conditions like diabetes and HIV.

Doctors can also work with local community-based and non-governmental organizations, and enlist community health workers as 'treatment supporters' to supervise and support the patient with treatment completion. To ensure treatment adherence, it is also important that doctors maintain some written record on what treatment was started, when, dosages, adverse reactions, results of follow-up lab tests, etc.

MONITORING TREATMENT SUCCESS

Weight of the patient should ideally be monitored on a monthly basis, and drug dosages adjusted to reflect the change in weight. The STCI recommendation states that 'response to therapy in patients with pulmonary tuberculosis, new as well as retreatment cases, should be monitored by follow-up sputum microscopy (one specimen) at the time of completion of the intensive phase of treatment and at the end of treatment.'[7]

MANAGEMENT OF ADVERSE EVENTS

Drug-induced hepatitis is the most common major adverse reaction associated with ATT. Severe nausea, jaundice or confusion should make the physician suspect the possibility of hepatitis. Advancing age and pre-existing liver disease are known risk factors, and special monitoring and care needs to be exercised in these groups of patients. All TB drugs should be stopped when hepatitis is suspected. The monitoring of the drug-induced hepatitis, and re-introduction of drugs is beyond the scope of this article and can be found elsewhere.[13]

Any reported visual impairment should warrant the stopping of ethambutol. Severe skin rashes may have to be treated by stopping all drugs and re-introducing them one at a time under observation, to identify the offending agent. Common minor side effects include nausea and anorexia, and can be minimized by taking the medications with small meals or just before bedtime. Joint pains caused by pyrazinamide can be treated with non-steroidal anti-inflammatory drugs, and pyridoxine supplements may be used to alleviate the mild tingling and numbness in the hands and feet that may be caused by isoniazid.

NOTIFICATION OF TB CASES

As per Government of India order and STCI recommendations,

CLINICAL HIGHLIGHTS

❑ GPs should follow the recommendations of the recently published Standards for TB Care in India (STCI) and the International Standards for TB Care (ISTC), and ensure that quality of TB care is aligned with best practices. All TB cases must be notified to local governmental authorities.

❑ Treatment of drug-sensitive TB involves the use of 4 drugs, and lasts 6 months. Rifamipicin, Isoniazid, Pyranzinamide and Ethambutol are prescribed for the initial two-month **intensive phase**, and Rifampicin and Isoniazid are continued for 4 more months in the **continuation phase** after the intensive phase

❑ Prescribing the drugs in the correct dosage is important for efficacy and the prevention of the emergence of drug resistant strains. The dosage is decided based on the weight of the patient.

❑ Every possible avenue should be explored to ensure adherence to treatment. These include identifying barriers to adherence, and the use of directly observed treatment (DOT), either physician administered, or with the help of facilitators, family or community support.

❑ Monitoring the response to treatment is an important component of care. All patients on ATT should be monitored by follow-up sputum microscopy at the time of completion of the intensive phase of treatment and at the end of treatment

❑ Minor adverse reactions to TB medications include nausea, gastric intolerance, neuropathy, and joint pains that can be managed symptomatically and do not warrant stoppage of medications. Major adverse reactions include hepatitis, severe skin reactions, optic neuropathy and renal failure. Symptoms and signs suggesting a major reaction should be treated by stoppage of drugs, close monitoring and careful re-introduction in accordance with published guidelines.

❑ Having a close contact with drug-resistant TB, having a relapse of TB after being declared cured, or being re-treated for TB after having defaulted on treatment in the past are risk factors for drug-resistant TB. Such patients, and those who fail treatment (have a positive sputum smear at 5 months) should be investigated for drug-resistant TB with culture and drug susceptibility testing of sputum.

❑ Since MDR-TB requires long-term and specialized management, patients should be referred to chest specialists.

'all health establishments must report all TB cases and their treatment outcomes to public health authorities (District Nodal Officer for Notification).'[7] By notifying all TB cases to the local health authorities, private practitioners can seek help from the RNTCP to help follow-up patients who default.

REFERRAL OF PATIENTS WITH SUSPECTED MDR-TB

All patients with risk factors for drug-resistance (e.g., patients with a history of previous TB treatment), must be investigated for MDR-TB using drug-susceptibility testing. Since MDR-TB requires long-term and specialized management, patients should be referred to chest specialists, either in the private sector, or in the public sector where free treatment is available under the programmatic management of drug-resistant TB.

In conclusion, GPs have a critical role to play in the control of TB at a community level, especially in India, where a majority of TB patients seek care in the private sector. Ensuring the best standards of TB treatment comprises the prescription of the right drugs in the right regimens, monitoring patients for signs of response to treatment and signs of adverse reactions to medications, and supporting the patient in maintaining adherence to treatment. ■

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CIS CME–Questions

Treatment of Pulmonary Tuberculosis:
What Every GP Should Know

Questions

1. **Which of the following is the correct drug regimen for a newly diagnosed patient with pulmonary tuberculosis?**
   a. 2 months of Streptomycin, Rifampicin, Isoniazid, Pyrazinamide and Ethambutol followed by 4 months of Rifampicin and Isoniazid
   b. 8 months of Rifampicin, Isoniazid and Ethambutol
   c. 2 months of Rifampicin, Isoniazid, Pyrazinamide and Ethambutol followed by 4 months of Rifampicin and Isoniazid
   d. 6 months of Rifampicin, Isoniazid, Pyrazinamide and Ethambutol

2. **Which of the following tests should be used to monitor the success of treatment for a patient with pulmonary tuberculosis?**
   a. Chest radiograph
   b. Sputum smear examination
   c. TB IgG, IgM antibodies
   d. TB Gold test (interferon-gamma release assay)

3. **When should one suspect the possibility of drug-resistant TB?**
   a. When the patient has been treated for TB in the past
   b. When the patient is in close contact with a patient who has drug-resistant TB
   c. When the patient has defaulted from treatment before the present illness
   d. All of the above

4. **Which of the following statements is true about intermittent treatment?**
   a. It is superior to daily treatment
   b. It can be given twice a week
   c. It should be prescribed only when treatment is supervised
   d. When prescribed, it must include an injectable drug

5. **Which of the following is false regarding adverse reactions to TB drugs?**
   a. Jaundice is a common adverse effect and is self-limiting
   b. Nausea is a common adverse effect, is usually self-limiting and can be treated with symptomatic management
   c. Joint pains are an adverse reaction to pyrazinamide and usually respond well to non-steroidal anti-inflammatory drugs
   d. The elderly and those with pre-existing liver disease are more susceptible to drug induced hepatitis

(See answers on the next page)

CIS CME–Answers

Treatment of Pulmonary Tuberculosis:
What Every GP Should Know
Questions on the previous page

Answers

1 **The correct answer is (c).** Injectable drugs are not part of the regimen for newly diagnosed pulmonary tuberculosis. The standard regimen for the treatment of TB lasts 6 months, with 4 drugs (Rifampicin, Isoniazid, Pyrazinamide and Ethambutol) prescribed in the first two months (intensive phase), and Rifampicin and Isoniazid continued for another 4 months (continuation phase). In India, because of high levels of INH resistance, the Standards for TB Care in India recommends the addition of ethambutol to the continuation phase.

2 **The correct answer is (b).** Sputum smear examination is recommended at the end of the intensive phase of treatment and at the end of treatment. Investigations for drug resistant TB need to be performed if the smear continues to be positive at 3 months. Treatment is considered to have failed if the smear at end of treatment is positive. Improvements in chest radiographs, while reassuring in the clinical context, are not specific enough to be used to monitor disease. TB IgG and IgM are serological tests that have been banned and have no role in the management of TB. IGRA (e.g., TB Gold) is a test to diagnose latent TB, and has no role in the diagnosis or monitoring of active disease.

3 **The correct answer is (d).** Relapse, retreatment and having a close contact with drug-resistant TB are important risk factors for drug-resistant TB, and questions pertaining to these risk factors are very important in the initial assessment of patients with TB.

4 **The correct answer is (c).** While intermittent treatment is an accepted modality of treatment, it is recommended only when compliance is ensured through direct supervision, and given for a minimum of three times a week. Twice-weekly regimens are not acceptable. Injectable drugs are not part of a standard intermittent treatment regimen for newly diagnosed pulmonary TB.

5 **The correct answer is (a).** Jaundice is a sign of hepatitis and warrants stoppage of all TB medications, and investigations for drug-induced hepatitis. It is more common in the elderly and in patients with pre-existing liver disease.

Let's Talk TB

A Series on Tuberculosis, A Disease That Affects Over 2 Million Indians Every Year

Extrapulmonary Tuberculosis:
New Diagnostics and New Policies

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Abstract

Clinical presentations of extrapulmonary TB (EPTB) is diverse, leading to missed cases and delayed diagnoses. Since the diagnosis of EPTB is often compromised by the paucibacillary nature of the disease, new diagnostic tools and policies have been eagerly awaited. At long last, new tools, and new policies are here. The International Standards for TB Care (ISTC) recommends that all patients, including children, who are suspected of having EPTB, should have appropriate specimens obtained from the suspected sites of involvement for microbiological and histological exam. The World Health Organization (WHO) has endorsed the use of Xpert MTB/RIF assay (Cepheid Inc., Sunnyvale, California), a cartridge based nucleic acid amplification test (NAAT), for EPTB. Xpert MTB/RIF is now considered a central test in the work-up of EPTB, and should be used along with existing tools such as microscopy, liquid cultures (which are the most sensitive technologies for MTB detection), and histopathology (biopsy) to arrive at the final diagnosis. Xpert is particularly useful in cerebrospinal fluid samples and in lymph node and other tissues. Once diagnosed, EPTB must be treated with standardized treatment regimens, as recommended by ISTC.

Key words: extrapulmonary tuberculosis; diagnosis; Xpert MTB/RIF; new policies

INTRODUCTION

Globally, tuberculosis (TB) remains a major public health concern with an estimated 10.4 million new cases and 1.7 million deaths reported in 2016.[1] India accounts for 25% of this global TB burden, and for a third of the 'missing cases' that do not get diagnosed or notified.[1]

Although reliable data from India are lacking, it is expected that 15 – 20% of all TB is extrapulmonary. Clinical presentations of extrapulmonary TB (EPTB) may be diverse, leading to missed cases and delayed diagnoses. The prevalence of EPTB is higher in HIV co-infected patients and children, two vulnerable groups that are well-known to represent even greater diagnostic challenges. Moreover, the consequences of some forms of ETPB (e.g., TB meningitis) may be life-threatening and thus timely diagnosis and initiation of appropriate therapy are crucial.

In India, there is a widespread belief, without population-based data, that TB is a major cause of infertility and this poses major diagnostic challenges for infertility specialists. Furthermore, chronic fevers of unknown origin are often suspected to be TB and treated empirically as such, but there are little data to verify if this is indeed the case.

Since the diagnosis of EPTB is often compromised by the paucibacillary nature of the disease, new diagnostic tools and policies have been eagerly awaited. At long last, new tools (i.e., Xpert MTB/RIF), and new policies are here. In 2013, the World Health Organization (WHO) endorsed the use of Xpert MTB/RIF assay (Cepheid Inc., Sunnyvale, California), a cartridge based nucleic acid amplification test (NAAT), for EPTB.[2] In March 2014, the 3rd edition of the updated International Standards for TB Care (ISTC)[3] and the first edition of the Standards for TB Care in India (STCI)[4] were released and both included new rec-

Table 1 – Accuracy of Xpert for EPTB samples and WHO recommendations on how Xpert should be used in each sample type

Sample	Sensitivity (compared to culture)	Specificity (compared to culture)	WHO Recommendations on the Use of Xpert
Cerebrospinal fluid (CSF)	81%	98%	Xpert is recommended as an initial diagnostic test in cerebrospinal fluid specimens for TB meningitis (strong recommendation given the urgency of rapid diagnosis).
Lymph nodes	83%	94%	Xpert is recommended as a replacement test for usual practice in specific non-respiratory specimens (lymph nodes and other tissues) for EPTB (conditional recommendation).
Pleural fluid	46%	99%	Pleural fluid is a suboptimal sample and pleural biopsy is preferred. While a positive Xpert result in pleural fluid can be treated as TB, a negative result should be followed by other tests.
Gastric lavage and aspirations	84%	98%	Xpert is recommended as a replacement test for usual practice in specific non-respiratory specimens (including gastric specimens) for EPTB (conditional recommendation).

Source of data: references 2 and 10
Definition of abbreviations: EPTB= Extra-pulmonary TB; WHO=World Health Organization; TB=Tuberculosis

ommendations for EPTB diagnosis.

The ISTC emphasizes the importance of seeking microbiological and histopathological diagnosis of EPTB, and underscores the critical need for collecting appropriate samples. ISTC recommends that all patients, including children, who are suspected of having EPTB, should have appropriate specimens obtained from the suspected sites of involvement for microbiological and histological exam.[3] In practice, this may mean collection of samples such as body fluids (cerebrospinal, pleural, ascitic fluid), lymph node and other tissues (e.g., endometrial tissue), and aspirates (e.g., gastric aspirate, pus). Patients being investigated for EPTB, particularly people living with HIV (PLHIV), should also receive sputum testing and a chest radiograph as they may also have asymptomatic or minimally symptomatic pulmonary TB (PTB).

In India, especially in the private sector, blood is popular as a sample for TB diagnosis.[5] This practice has no biological or clinical rationale, as there is currently no accepted, validated biomarker in the blood that can detect EPTB or PTB. Thus, there is no role for blood-based antibody tests, or for blood-based interferon-gamma release assays (IGRAs) such as TB Gold and TB Platinum. IGRAs were designed to diagnose latent TB infection.[6] Like the tuberculin skin test (i.e., Mantoux), they cannot distinguish between latent infection and active pulmonary or extrapulmonary disease.[7,8] The Indian government banned serological antibody tests in 2012, and STCI and ISTC discourage the use of IGRAs for active TB diagnosis.[3,4]

Both ISTC and STCI now recommend the Xpert MTB/RIF assay for PTB and EPTB in adults and children.[4,7] The Xpert MTB/RIF assay allows for rapid detection of MTB DNA along with confirmation of rifampin resistance using rpoB gene mutation testing. It is automated, very easy to use and produces results within 2 hours.

Based on an updated Cochrane systematic review, when used as an initial test replacing smear microscopy for pulmonary TB, Xpert MTB/RIF has an overall sensitivity of 88% and pooled specificity of 98%, as compared to culture.[9] The pooled sensitivity is 98% for smear-positive, culture-positive cases and 68% for smear-negative cases; the pooled sensitivity is 80% in PLHIV. Xpert MTB/RIF, when used as an initial test replacing phenotypic drug susceptibility testing, detects 95% of rifampicin-resistant TB cases with specificity of 98%.[9]

More recently, evidence has accumulated on the accuracy of Xpert MTB/RIF for various forms of EPTB. This was summarized in a recent meta-analysis by Denkinger and colleagues[10] and is shown in **Table 1**, along with the latest WHO recommendations on EPTB, which are reiterated in the ISTC.

Thus, Xpert MTB/RIF should now be considered a central test in the work-up of EPTB, and should be used along with existing tools such as microscopy, liquid cultures (which are the most sensitive technologies for MTB detection), and histopathology (biopsy) to arrive at the final diagnosis. WHO has produced stan-

dard operating procedures on how to process various types of EPTB samples, and laboratories should implement these procedures to ensure quality.[11] It is important to note that Xpert MTB/RIF should not be performed on blood samples. Once diagnosed, EPTB must be treated with standardized treatment regimens, as recommended by STCI and ISTC.

While new tools like Xpert and new policies like STCI and ISTC are now available, it is important to ensure that these are widely used in the private sector, which manages nearly half of all TB in India. In fact, EPTB in India may be managed predominantly in the private sector. It is well known that TB diagnostic and treatment practices in the private sector are highly variable and often do not confirm to national or international standards.[5,12-14] This is why new initiatives like STCI should be widely promoted in the private sector, along with appropriate education and monitoring of quality of TB care.[14]

A big hurdle for the use of high quality, WHO-endorsed TB tests like Xpert and liquid cultures has been their high cost in the private market.[15] This is because WHO-endorsed tests are available at specially negotiated low prices only to the public sector, and import duties also add to the costs. In addition, financial incentives and laboratory margins further increase the costs to put them beyond the reach of most patients.

Fortunately, in 2013 a new initiative was launched to improve the affordability of WHO-endorsed TB tests. Initiative for Promoting Affordable, Quality TB tests (IPAQT www.ipaqt.org) is a coalition of private labs in India, supported by non-profit agencies such as the Clinton Health Access Initiative, that has made several WHO-approved tests available at affordable prices to patients in the private sector.[15-17] Labs in IPAQT have access to lower, concessionary prices for the quality tests in exchange of their commitment to pass on the lower prices to patients.

Due to IPAQT, which uses a high-volume, low-margin model to drive costs down, the cost of Xpert is now reduced to Rs 2200 (maximum price labs can charge patients). The line probe assay (Hain Genotype MTBDRplus, Hain Lifescience, Germany) is now available at Rs 1800. Liquid cultures (e.g., MGIT from BD Diagnostics) are available at Rs 900. These prices are approximately 30 to 50% less than the private market prices before IPAQT was launched. TB cases diagnosed are notified to the government and all labs are accredited. Since its launch, IPAQT has steadily grown – with over 170 labs across India now providing these tests at affordable prices.

In conclusion, patients with all forms of TB deserve a complete and patient-centric solution.[18] Improving the quality of TB care and expanding access to rapid, accurate diagnosis for all forms of TB, and prompt initiation of appropriate therapy is an ethical imperative and must be prioritized. It is our hope that new tools like Xpert, and new policies like ISTC and STCI will facilitate changes in practice and improve the quality of TB care for patients in India, regardless of whether they are managed in the public or the private sector.

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CIS CME–Questions

Extrapulmonary Tuberculosis:
New Diagnostics and New Policies

Questions

1. **Which of the following samples is not appropriate for a case of suspected tuberculous pleural effusion?**
   a. Blood
   b. Pleural fluid
   c. Pleural biopsy
   d. Sputum

2. **Which of the following diagnostics tests is endorsed by WHO for extrapulmonary TB?**
   a. Interferon-gamma release assay (IGRA)
   b. Tuberculin skin test (Mantoux)
   c. Xpert MTB/RIF
   d. Serological (antibody) TB tests

3. **Which of the following tests are banned by the government of India:**
   a. Sputum smear microscopy
   b. Polymerase chain reaction (PCR)
   c. Interferon-gamma release assay (IGRA)
   d. Serological (antibody) TB tests

4. **Interferon-gamma release assays (e.g., TB Gold) and Mantoux skin test cannot distinguish between latent infection and active (pulmonary or extrapulmonary) disease. True or False?**
   a. True
   b. False

5. **Of the following tests, which has the highest sensitivity for TB?**
   a. Smear microscopy
   b. Tuberculin skin test
   c. Liquid cultures
   d. Interferon-gamma release assay (IGRA)

6. **In which of the following specimens does Xpert MTB/RIF have the lowest sensitivity?**
   a. Lymph nodes
   b. CSF
   c. Gastric aspirates
   d. Pleural fluid

(See answers on the next page)

CIS CME–Answers

Extrapulmonary Tuberculosis:
New Diagnostics and New Policies
Questions on the previous page

Answers

1. **The correct answer is (a).** There is no validated blood test for pleural or any form of extrapulmonary tuberculosis. Other samples listed are useful to collect.

2. **The correct answer is (c).** In 2013, WHO endorsed the use of Xpert MTB/RIF for extrapulmonary TB.

3. **The correct answer is (d).** The Indian Government has banned the use, sale and import of all commercial serological (antibody-detection) TB tests. This includes ELISA as well as rapid antibody tests. The ban applies to domestic as well as imported serodiagnostics kits. The ban is based on a WHO policy that strongly recommends against the use of serological, antibody tests for TB. The International Standards for TB Care, and Standards for TB Care in India also discourage the use of serological TB tests.

4. **The correct answer is TRUE.** Neither Mantoux nor TB Gold can separate latency from active TB disease. Thus, they are discouraged for active TB diagnosis.

5. **The correct answer is (c).** Liquid cultures have the highest sensitivity.

6. **The correct answer is (d).** Xpert does not have high sensitivity in pleural fluid samples, and therefore should not be used alone. It should be used in combination with other tests such as pleural fluid/tissue cultures and biopsy.

Let's Talk TB

A Series on Tuberculosis, A Disease That Affects Over 2 Million Indians Every Year

Management of Latent Tuberculosis Infection

Madhukar Pai, MD, PhD—Author and Series Editor
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Abstract

Most individuals who get exposed to Mycobacterium tuberculosis (MTB) manage to eliminate or contain the infection using host T-cell immune defenses. However, some MTB bacilli may remain viable (latent) and "reactivate" later to cause active TB disease. This state is called Latent TB Infection (LTBI). Identification and treatment (i.e. preventive therapy or prophylaxis) of LTBI can substantially reduce the risk of development of active disease (by as much as 60%). However, because 40% of Indians are latently infected, LTBI screening must be restricted to specific high risk populations in India, where the benefits of LTBI treatment outweigh any risks. These include people living with HIV, adult and child contacts of pulmonary TB cases, patients initiating anti-tumour necrosis factor (TNF-alpha) treatment, patients with end stage renal failure on dialysis, patients preparing for organ or haematologic transplantation, and patients with silicosis. While either tuberculin skin test (Mantoux) or interferon-gamma release assays (e.g., TB Gold) can be used for LTBI screening, it is important to make sure that these tests are not used for active TB diagnosis. For persons with symptoms or abnormal chest x-rays, physicians should order smears, cultures, and molecular tests (e.g., Xpert MTB/RIF). If LTBI is diagnosed, then physicians must rule-out TB disease with chest x-rays before starting one of the recommended drug regimens. It is important to ensure adherence, and provide adequate counseling to ensure that patients do not stop therapy prematurely..

Key words: tuberculosis; treatment; latent TB infection, Mantoux test, IGRA

INTRODUCTION

Most individuals who get exposed to *Mycobacterium tuberculosis* (MTB) manage to eliminate or contain the infection using host T-cell immune defenses. However, some MTB bacilli may remain viable (latent) and "reactivate" later to cause active TB disease. This state is called Latent TB Infection (LTBI).

Although LTBI and active TB disease are part of a dynamic spectrum,[1] people with LTBI are asymptomatic and not infectious. For example, nearly 50% of doctors and healthcare workers in India will test positive on the Mantoux tuberculin skin test, but a majority will not display any TB symptoms, or develop active TB disease.[2] Such individuals, presumably, have LTBI. However, some healthcare workers may go on to develop symptoms, and if found to have active TB require the standard 4-drug short course anti-TB therapy.

Identification and treatment (i.e., preventive therapy or prophylaxis) of LTBI can substantially reduce the risk of development of active disease (by as much as 60%), and is an important TB control strategy in low-TB incidence settings where reactivation disease usually accounts for the majority of non-imported TB disease.[3] For example, LTBI screening and treatment is a major component of TB control programs in both USA and Canada, and large numbers of individuals are tested for LTBI and treated with isoniazid for 9 months. However, LTBI screening and treatment is rarely done in high TB burden countries such as India. This is because nearly 40% of the population is estimated to have latent TB infection.

The goal of testing for LTBI is to identify individuals who are at

Figure 1 – Tuberculin skin test being administered, using the Mantoux method.

Figure 2 – QuantiFERON TB Gold In Tube is an ELISA-based IGRA test for TB infection. It is not recommended for active TB detection.

increased risk for the development of active TB; these individuals would benefit most from treatment of LTBI. There is no diagnostic gold standard for LTBI and all existing tests are immunological tests that provide indirect evidence of sensitization of the host to TB antigens.

There are two available tests for identification of LTBI: tuberculin skin test (TST) and interferon-gamma release assays (IGRA). TST is usually performed using the Mantoux skin test method (**Figure 1**), and purified protein derivative (PPD) is the antigen injected intradermally. Skin induration is read after a period of 48 – 72 hours. In India, a 10 mm induration is considered positive.

IGRAs are done *in vitro*, and instead of PPD, they use highly specific peptides from two main antigens – early secreted antigenic target (ESAT6) and culture filtrate protein (CFP10). Commercial IGRAs include QuantiFERON-TB Gold In Tube (Qiagen, USA) (**Figure 2**), and T-SPOT. TB (Oxford Immunotec, UK). Both TST and IGRA depend on cell-mediated immunity (memory T-cell response), and a positive result suggests that the patient has been exposed and sensitized to MTB in the past.

A detailed recent review of these tests is available elsewhere.[4] Briefly, published data suggests that both TST and IGRA are acceptable, but somewhat imperfect tests. Both represent indirect markers of MTB exposure and measure a cellular immune response to MTB (read as mm induration with the TST, and amount of interferon-gamma released by T-cells in IGRAs). Neither test can accurately differentiate between LTBI and active TB. Neither test can resolve the various stages within the spectrum of MTB infection.

Both TST and IGRA have reduced sensitivity in immunocompromised patients (e.g., people living with HIV/AIDS), and have low predictive value for progression to active TB. In other words, a majority of individuals with positive TST or IGRA results will not progress to active TB disease.[5]

Tuberculin skin test surveys in India show a very high annual risk of TB infection.[6] Given the very high TB burden of active TB in India, it is not surprising that nearly 40% of Indians are estimated to be latently infected.[7] Given the large number of latently infected individuals in the country, the Revised National TB Control Program (RNTCP) does not give priority to LTBI detection and treatment in the public sector. This is true for most high TB burden countries around the world.

For high burden countries like India, what should be the approach towards management of LTBI? In 2014, WHO published its first comprehensive guideline on management of latent TB infection.[8] This guideline offers a clear, evidence-based algorithm (**Figure 3**).[8]

As shown in the algorithm, WHO recommends that only selected risk groups should be evaluated for LTBI.[8] These include people living with HIV, adult and child contacts of pulmonary TB cases, patients initiating anti-tumour necrosis factor (TNF-alpha) treatment, patients with end stage renal failure on dialysis, patients preparing for organ or haematologic transplantation, and patients with silicosis. The rationale for giving priority to these subgroups is that they are at very high risk of progressing from latent infection to active disease, and this could be prevented by treating LTBI.

If an individual has any of the above risk factors, the WHO algorithm requires that they be assessed for TB symptoms. If any TB symptom is present (e.g., cough, fever, weight loss, hemoptysis, night sweats), then the focus should be on diagnosing active TB using WHO

and RNTCP-endorsed microbiological tests such as smear microscopy, TB cultures and molecular tests such as Xpert MTB/RIF (GeneXpert, Cepheid Inc, USA), and line probe assays such as Genotype MTBDRplus (Hain LifeScience, Germany). A chest x-ray can also be used as part of the work-up for active TB. If the individual has no symptoms, then WHO recommends that either TST or an IGRA be used to test for LTBI in high-income and upper middle-income countries with estimated TB incidence less than 100 per 100000. TST is preferred and IGRA should not replace TST in low-income and other middle-income countries.[8]

If either TST or IGRA is positive, then the next step is to rule out active disease, before starting LTBI treatment. This is done by getting a chest x-ray. If the x-ray shows any abnormalities, then it is critical to investigate for active TB, using smear microscopy, TB cultures and molecular tests. If the x-ray is normal, then the likelihood of active TB is very low, and LTBI treatment can be initiated.

What are the drug regimens available for LTBI treatment? Unlike active TB where 4 drugs are required in the intensive phase, the burden of bacteria in LTBI is quite low. So, even a single TB drug is sufficient. As shown in the WHO algorithm, treatment options recommended by WHO include 6 to 9 months of isoniazid, 3-month regimen of weekly rifapentine plus isoniazid, or 3–4 months isoniazid plus rifampicin, or 3–4 months rifampicin alone.[8] All regimens are known to be efficacious, but adherence can be poor with longer regimens such as 9 months of isoniazid.[3] Rifampicin containing regimens may be more suitable in populations with a high background level of isoniazid mono-resistance.

Regardless of the regimen used for LTBI, it is important to ensure adherence, and provide patients adequate counseling about why they are being treated for LTBI (despite not having symptoms), likely adverse events, and monthly follow-up visits. The risk of toxicity is highest with isoniazid, especially in older individuals, and those who consume alcohol.[3]

In India, there is concern that tests such as Mantoux and IGRAs (e.g., TB Gold, TB Platinum) are being misused for active TB diagnosis.[9] The WHO algorithm clearly shows that when doctors suspect active TB, they

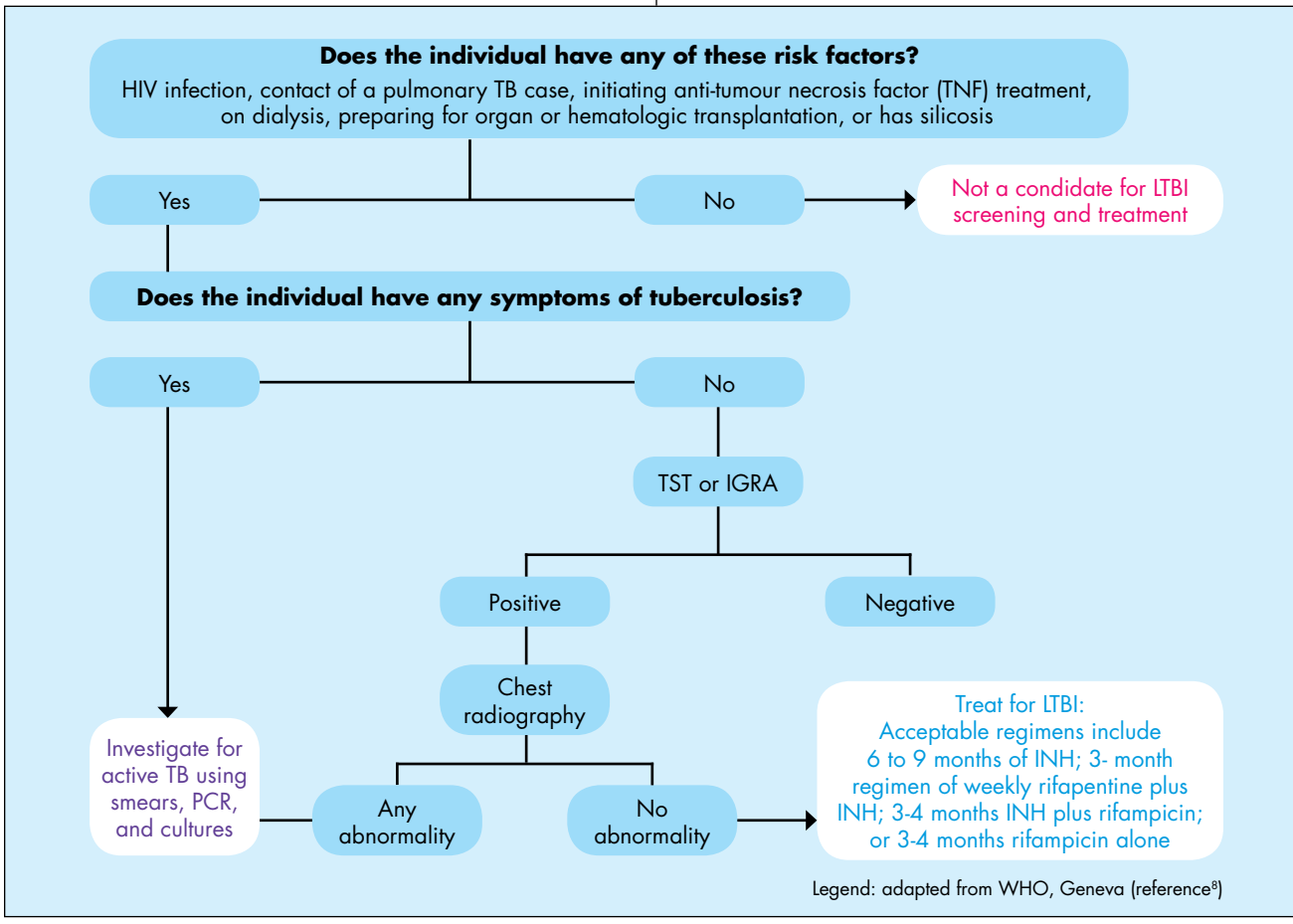

Figure 3 – WHO algorithm for latent TB infection management.

Table 1– Recommended drug dosages for acceptable LTBI treatment regimens

Drug regimen	Dose per body weight	Maximum dose
Daily **Isoniazid** alone for 6 or 9 months	Adults = 5mg/kg Children = 10 mg/kg	300 mg
Daily **Rifampicin** alone for 3-4 months	Adults = 10 mg/kg Children = 10 mg/kg	600 mg
Daily **Isoniazid** plus **Rifampicin** for 3-4 months	**Isoniazid** Adults = 5 mg/kg Children = 10 mg/kg **Rifampicin** Adults and children = 10 mg/kg	**Isoniazid** = 300 mg **Rifampicin** = 600 mg
Weekly **Rifapentine** plus **Isoniazid** for 3 months (12 doses)	Adults and children **Isoniazid:** 15 mg/kg **Rifapentine** (by body weight): 10.0-14.0 kg = 300 mg 14.1-25.0 kg = 450 mg 25.1-32.0 kg = 600 mg 32.1-49.9 kg = 750 mg	**Isoniazid** = 900 mg **Rifapentine** = 900 mg

Legend: adapted from WHO, Geneva (reference[8])

should be testing for active TB, not screening for LTBI. In fact, the Standards for TB Care in India (STCI) clearly states that both TST and IGRAs should not be used for the diagnosis of active TB in high endemic settings like India.[10] If IGRAs are used for active TB diagnosis, this will result in significant over-diagnosis of TB, because of the high background prevalence of LTBI in India. In children, STCI suggests that the Mantoux test may have some value as a test for infection, in addition to chest x-rays, symptoms, history of contact, and other microbiological investigations (e.g., gastric juice acid fast bacilli and Xpert MTB/RIF).[10]

In conclusion, LTBI screening must be restricted to specific high risk populations in India, where the benefits of LTBI treatment outweigh any risks. While either TST or IGRA can be used for LTBI screening, it is important to make sure that these tests are not used for active TB diagnosis. For persons with symptoms or abnormal chest x-rays, physicians should order smears, cultures, and molecular tests (these tests are now available in the public as well as the private sector in India). If LTBI is diagnosed, then physicians must rule-out TB disease with chest x-rays before starting one of the recommended drug regimens. It is important to ensure adherence, and provide adequate counseling to ensure that patients do not stop therapy prematurely.

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CIS CME–Questions

Management of Latent Tuberculosis Infection

Questions

1 What is the estimated prevalence of latent TB infection in India?

a. 5%
b. 10%
c. 40%
d. 80%

2 Which of the following tests can be used to screen for latent TB infection?

a. GeneXpert (Xpert MTB/RIF)
b. Sputum smear examination
c. TB IgG, IgM antibodies
d. Mantoux (tuberculin skin test)

3 Which of these high-risk populations should be targeted for LTBI screening and treatment?

a. People living with HIV/AIDS
b. Child contacts of pulmonary TB cases
c. Patients initiating anti-tumour necrosis factor (TNF-alpha) treatment
d. Patients with end stage renal failure on dialysis
e. All of the above

4 Which of the following statements is TRUE about interferon-gamma release assays (e.g., TB Gold)?

a. IGRAs cannot separate latent infection from active TB, and, therefore, not recommended for active TB detection
b. IGRAs are skin tests for latent infection
c. IGRAs are useful for diagnosing active, pulmonary TB
d. IGRAs are banned in India

5 Which of the following drug regimens are NOT recommended for latent TB infection?

a. 6 to 9 months of isoniazid
b. 3-month regimen of weekly rifapentine plus isoniazid
c. 3–4 months isoniazid plus rifampicin
d. 3–4 months rifampicin alone
e. Isoniazid, rifampicin, pyrazinamide, and ethambutol (HRZE) for 2 months, followed by isoniazid and rifampicin (HR) for 4 months

(See answers on the next page)

CIS CME–Answers

Management of Latent Tuberculosis Infection

Questions on the previous page

Answers

1. **The correct answer is (c).** An estimated 40% of the Indian population is estimated to be latently infected, using tuberculin surveys.

2. **The correct answer is (d).** The tuberculin skin test, using Mantoux technique, is one of the two accepted tests for latent TB infection screening. The other test is interferon-gamma release assays (e.g., TB Gold)

3. **The correct answer is (e).** Latent TB screening should be restricted to high-risk groups. These include people living with HIV and AIDS, adult and child contacts of pulmonary TB cases, patients initiating anti-tumour necrosis factor (TNF-alpha) treatment, patients with end stage renal failure on dialysis, patients preparing for organ or haematologic transplantation, and patients with silicosis.

4. **The correct answer is (a).** IGRAs cannot separate latent infection from active TB, and, therefore, not recommended for active TB detection. This is also true for Mantoux skin test. Both IGRAs and TST should be restricted to LTBI screening, and should not be used for active TB diagnosis. In children, Mantoux test may have some value as a test for infection, in addition to chest x-rays, symptoms, history of contact, and other microbiological investigations (e.g., gastric juice acid fast bacilli and Xpert MTB/RIF).

5. **The correct answer is (e).** The HRZE drug regimen is meant for treating active tuberculosis. For latent TB infection, treatment options recommended by WHO include 6 to 9 months of isoniazid, 3-month regimen of weekly rifapentine plus isoniazid, or 3–4 months isoniazid plus rifampicin, or 3–4 months rifampicin alone.

Let's Talk TB

A Series on Tuberculosis, A Disease That Affects Over 2 Million Indians Every Year

Management of HIV and Tuberculosis:
What Every GP Should Know

Faiz Ahmad Khan, MD, MPH—Co-author
Madhukar Pai, MD, PhD—Author and Series Editor

Abstract

Tuberculosis (TB) is the leading cause of morbidity and mortality in people living with HIV (PLWH). The epidemiologic link between HIV and TB is strong even in a low HIV prevalence country such as India – hence all Indian physicians that see patients with suspected or confirmed TB should understand how to approach TB diagnosis and treatment among PLWH, even if they are not working in a community where HIV infection is common. This article provides general practitioners with a concise and practical overview of TB screening, prevention, diagnosis and treatment, in PLWH.

Key words: HIV/AIDS, TB screening and prevention, antiretrovirals, treatment

INTRODUCTION

Tuberculosis (TB) remains the leading cause of morbidity and mortality in people living with HIV (PLWH).[1] In 2013, 13% of all cases of TB in the world occurred in PLWH, and this group accounted for 27% of TB deaths.[2]

India is home to 2.1 million PLWH—the third largest population of HIV-infected persons in the world. While the overall prevalence of HIV in India is estimated to be 0.27%,[3] PLWH account for 5.7% of incident TB cases.[2] In India, any general practitioner that sees patients with suspected or confirmed TB should have a solid understanding of how the presence of HIV infection affects the clinical presentation, diagnosis, and treatment of TB. This is true even for physicians who primarily practice in a low HIV prevalence community. Indian general practitioners working with subpopulations where HIV infection is common should also have a firm grasp on how to approach TB screening and prevention in PLWH.

This review article provides a concise overview of the critical aspects of TB management in PLWH. The keys to successful TB screening, prevention, diagnosis and treatment in PLWH can be found in the Standards for Tuberculosis Care in India (STCI)[4] and various World Health Organization guidelines,[5-10] and the reader is referred to these documents for more detailed guidance.

HIV-TB BASICS

There are two clinical forms of TB infection: latent and active. In people with latent TB infection, bacilli are in a "dormant" state – kept in check by the host's immune system, the bacilli are essentially not replicating, and are not causing tissue destruction.[11] People with latent TB infection are not contagious. In contrast to latent infection, active TB is a disease state in which the bacilli are actively replicating and inducing immune-mediated tissue destruction.

While active TB can occur in a number of anatomical locations, the most common are the lungs—i.e., pulmonary TB. People with active pulmonary TB, and also those with TB of the upper airways, can transmit infection to others. Without treatment, active TB can be fatal. Once someone has acquired latent TB infection, the probability that they will subsequently develop ac-

tive TB depends on a number of factors, such as how recently the person was infected and the presence of co-morbid conditions.[11]

THE IMPACT OF HIV ON PROGRESSION FROM LATENT TB INFECTION TO ACTIVE TB

HIV infection is one of the strongest risk factors for progression from latent to active TB.[12-15] A common misunderstanding is that the risk of progression from latent to active TB only increases in PLWH if the CD4 count has fallen below 200 cells/mm^3. In fact, the risk of active TB starts to increase within months of becoming infected with HIV, before the CD4 cell count has fallen below 200 cells/mm^3.[14] If HIV infection continues to weaken the immune system— i.e., in the absence of effective antiretroviral therapy (ART) — the risk of progression from latent to active TB will continue to rise.[14] It should be noted that while ART greatly lowers the risk of progression from latent to active TB in PLWH,[16] the risk of TB remains elevated compared to the risk in non-HIV infected populations.[17] This is why TB screening and prevention are important for all PLWH, regardless of their CD4 count and whether or not they are on ART.

THE IMPACT OF HIV ON THE CLINICAL MANIFESTATIONS OF ACTIVE TB

Clinical manifestations of active TB in PLWH depend on the degree of immunosuppression.[18,19] In PLWH, active TB can present with classic symptoms – fevers, cough, sputum production, hemoptysis, weight loss, and night sweats. However, with advanced immunosuppression, active TB can be minimally symptomatic. Hence, the presence of any of these classic symptoms should trigger further diagnostic evaluation of TB—even if the symptoms are mild—in a high TB incidence setting such as India. While pulmonary TB is the most common form of active TB in PLWH, in patients with advanced immunosuppression, extrapulmonary disease is also common.[20,21] Extrapulmonary TB can occur in almost any organ system; common sites include lymph nodes, the pleural space, CNS, abdomen, bones/joints, and genitourinary system.

THE IMPACT OF HIV ON THE DIAGNOSIS OF ACTIVE TB

In patients with advanced immunosuppression, most microbiologic tests for active TB are less sensitive (i.e., will have a higher false-negative rate). This is true for sputum smear microscopy,[22, 23] and also for more advanced PCR-based tests, such as GeneXpert (Xpert MTB/RIF).[24] In general, sputum smear microscopy is not an adequate test for ruling out pulmonary TB in PLWH because the rate of false-negative results is high—even when more than one smear has been performed[23]—and the risk of mortality from untreated TB is very elevated in PLWH.

Figure 1 – Xpert MTB/RIF (GeneXpert) is the recommended TB test for people living with HIV/AIDS

The GeneXpert (Xpert MTB/RIF) assay is a much more sensitive test than sputum smear microscopy, hence, the STCI recommend GeneXpert as the front-line test for TB in PLWH (**Figure 1**). However, a false-negative GeneXpert result is seen in ~20% of PLWH who have active TB;[24] hence, if the first GeneXpert result is negative (i.e. "MTB not detected"), and TB is still suspected, it is reasonable to perform GeneXpert on a second sputum sample in order to lower the likelihood of missing a case of active TB in PLWH. The STCI also recommends that all persons in whom pulmonary TB is suspected should have two sputa submitted for microbiologic analysis, at least one of which should be an early morning sample.[4] Ideally these should be sent for both smear microscopy and TB culture. Even though it can take several weeks before cultures confirm or exclude TB, specimens should always be sent for culture—as it is the most sensitive and specific test for TB, even in PLWH.

Chest x-ray (CXR) is a sensitive test for identifying active pulmonary TB in PLWH—even in patients with minimal symptoms. In PLWH, the presence of any CXR abnormality—including those that are not "classic" for TB—should raise the possibility that active TB is present; this is particularly true in patients with advanced immunosuppression.[25,26] When a CXR abnormality is present, all efforts should be made to send sputum for microbiologic evaluation for TB (as described above), but consideration should also be given to other pulmonary infections seen in PLWH. In patients with "classic"

CXR findings of pulmonary TB, it may be reasonable to empirically start treatment for active TB while awaiting results of confirmatory testing. In PLWH with very advanced immunosuppression, active pulmonary TB can be present even if the CXR is normal in appearance[27,28]—hence, in such patients, a normal radiograph should not preclude microbiologic analysis of sputum as described above.

Microbiologic confirmation of extrapulmonary TB is challenging for two reasons. First, it is often difficult to obtain specimens. Second, when tissue or fluid is obtained, the rate of false-negative microbiology results is high – especially for smear microscopy. Nevertheless, all efforts should be made to obtain specimens for TB cultures and GeneXpert to confirm the diagnosis when extrapulmonary TB is suspected.[10] When TB meningitis is suspected, the WHO recommends cerebrospinal fluid analysis by the GeneXpert assay as the preferred front-line test.[10] GeneXpert can also be used to test fluid obtained from other sites (e.g., lymph node aspirates, gastric lavage).[10] Empiric treatment for extrapulmonary TB may be reasonable—and should not be delayed, particularly when TB meningitis is suspected—in PLWH with advanced immunosuppression in whom diagnostic confirmation may be difficult.

THE IMPACT OF HIV ON ACTIVE TB OUTCOMES

As compared to their HIV-negative counterparts, PLWH who have active TB are more likely to experience poor TB treatment outcomes. In particular, HIV infection greatly increases the risk of mortality,[29-32] and acquisition of resistance to anti-TB medications.[32-35] Additionally, PLWH who are cured of active TB are at increased risk of TB relapse. By providing appropriate medical management—including early diagnosis and institution of effective HIV and TB treatment—general practitioners can help mitigate many of these risks and give their patients with active TB and HIV infection the best chance of survival and relapse-free TB cure, and also prevent the devastating consequences of acquired TB drug-resistance.

HIV AND DRUG-RESISTANT TB

PLWH are at increased risk of developing drug-resistant forms of TB—in particular, rifampicin resistance.[32-35] The reasons for this are unclear—interactions with other medications and malabsorption may contribute. Drug-resistant TB and HIV are a deadly combination—particularly in the presence of multidrug-resistant (MDR) or extensively drug resistant (XDR) strains. A recent hospital-based outbreak of XDR-TB in PLWH was associated with a mortality rate of close to 100%.[36] Because of this, drug susceptibility testing should be performed for all PLWH who have active TB at the start of therapy—even in those that have never before received anti-TB medications—in order to reduce delays in the diagnosis of drug-resistance. Drug susceptibility tests should be repeated for patients on treatment if there is suspected failure, or lack of improvement. The STCI recommends that all PLWH who have active TB be tested for drug-resistance to isoniazid and rifampin with rapid molecular drug-susceptibility tests as the method of choice.[4]

MANAGEMENT OF HIV-TB CO-INFECTION: FREQUENTLY ASKED QUESTIONS

I am seeing a patient and I suspect they have active TB. Should I test them for HIV infection?

Yes. Because of the strong epidemiologic link between HIV and TB, all patients in whom TB is suspected should be tested for HIV infection, even before the diagnosis of TB has been confirmed. In fact, in high TB burden areas, active TB is often the presenting manifestation of HIV-infection.

My patient has been diagnosed with active TB. Should I test them for HIV infection?

Yes. As stated earlier—all patients with active TB should be tested for HIV infection.[4]

Is there anything I can do to lower the risk of infection by *Mycobacterium tuberculosis* in my patients that are PLWH?

Yes. Many people become infected with TB in healthcare settings—including hospitals and clinics—because they are more likely to encounter people with undiagnosed active TB in these locations. Simple TB infection control measures can substantially reduce the risk that TB transmission will occur in such settings.[5] Administrative measures that you can institute in your clinic to reduce the risk of TB transmission include: having a clinic attendant monitor all people in the waiting room for cough, ensuring that anyone who is coughing wears a simple mask, or covers their mouth and nose with a cloth. Environmental measures can include ensuring that windows are kept open to maximize ventilation.

Should I screen PLWH for active TB? If so, how?

Yes! The WHO recommendation, echoed in the STCI, is that all PLWH should be screened for active TB using a symptom-based questionnaire, and, if resources permit, a CXR.[4,9] The screening should be performed at the time the patient is enrolled into care and repeated at every clinical visit. For symptom-based TB screening, the WHO recommends assessing for the presence of

the following: fevers, night sweats, cough, and weight loss. The presence of at least one symptom means that active TB should be suspected and further diagnostic evaluation is required. If you work in a clinic or region where TB prevalence amongst PLWH is very elevated (e.g., greater than 5%), then all efforts should be made to ensure that a CXR is obtained for TB screening in addition to the symptom assessment.[9] Under such circumstances, CXR should be performed regardless of the presence or absence of symptoms in order to lower the likelihood of missing a case of active TB in someone that is asymptomatic (e.g., early in the course of active TB). If a CXR is performed in addition to the symptom-based questionnaire, then the presence of any abnormality means that active TB should be suspected and further diagnostic testing is warranted—this is true even if the person being screened is asymptomatic. Once a PLWH has been identified as a presumed TB case, all efforts should be made to confirm or exclude active TB using a microbiologic test (**see below**).

If my patient has HIV-infection, and is showing symptoms of active TB, which test should I order?

In addition to CXR, a GeneXpert test is the best microbiological test to order in those with HIV-infection. According to WHO, Xpert MTB/RIF should be used as the initial diagnostic test in adults and children presumed to have HIV-associated TB.[4,10]

How can I prevent the development of active TB in PLWH?

The two most important and highly effective interventions that lower the risk of active TB in PLWH are ART—which has been shown to reduce the risk of TB in PLWH regardless of their CD4 count[16,37]—and isoniazid preventive therapy (IPT).[16,37] Prior to starting IPT, patients must be screened to rule out active TB—this is because the provision of isoniazid alone to someone with active TB will result in the development of isoniazid-resistant TB. Hence IPT initiation is typically closely tied to TB screening: first, PLWH are screened to rule out active TB (as described above), and if the screening is negative, they initiate IPT. IPT should be given for at least 6 to 9 months.[4]

Apart from choosing the right drugs for TB and HIV—are there other things I can do to improve TB outcomes in my co-infected patients?

Absolutely! Minimizing the delay to starting effective TB treatment is crucial—for all patients with active TB, but especially for those co-infected with HIV. It is also important to make all efforts to confirm the diagnosis of TB through microbiologic tests.[4] In order to avoid delays in treatment caused by delays in diagnosis, it may be reasonable to initiate TB treatment before results of your diagnostic evaluation have returned. The GeneXpert assay can be particularly useful in minimizing diagnostic delays as it provides results within a few hours; it has the added advantage of simultaneously testing for active TB and also the presence of resistance to rifampicin (which is a good marker of MDR-TB).

What anti-TB drug regimen should be used to treat active TB in PLWH?

PLWH with active pulmonary TB that are at low-risk of drug-resistant TB should be treated with an intensive phase of two months of isoniazid, rifampin, pyrazinamide and ethambutol (HRZE); followed by a four-month continuation phase of isoniazid and rifampin (HR). During both the intensive and continuation phases, treatment should be given daily (at least five days per week)—this is because intermittent treatment has been associated with increased risks of treatment failure and acquired drug resistance in PLWH.[4] There is some evidence to suggest that prolonging the continuation phase by 2 to 3 months – such that total treatment duration is 8 to 9 months—may reduce the risk of relapse.[38,39] Patients with extrapulmonary TB should be referred to a TB specialist as optimal management will depend on the site of disease—however, such referrals should not delay the initiation of TB treatment as delayed TB treatment increases the risk of mortality, particularly in PLWH.

In PLWH whose ART regimens contain protease inhibitors, rifabutin can be used in lieu of rifampin to minimize drug interactions.

I have just diagnosed active TB in an HIV-infected patient—they are not on ART, should I initiate ART? If so, when?

In general, because of toxicity and drug interactions, it is better for specialists to manage patients who need to be on ART and anti-TB therapy simultaneously. ART is indicated for all PLWH who have active TB, regardless of their CD4 count—as it lowers the risk of death.[4,6] For a number of years, there was clinical equipoise about whether the initiation of ART should be delayed until the end of TB treatment— the concern was that once the immune system started to reconstitute, the inflammatory response elicited by the presence of TB bacilli could result in clinical deterioration. However, a series of randomized controlled trials have addressed this question and provided clear-cut evidence of improved survival in patients that initiate ART within 8 weeks of starting TB treatment.[40,41] Hence the current recommendation is for PLWH with active TB that are not on ART to initiate active TB treatment first, and to subsequently initiate ART as soon as possible and with a maximum delay of 8 weeks from the start of TB treatment.[4,6]

I have just diagnosed active TB in a patient

with HIV infection who is already on ART— what TB treatment should I initiate?

As suggested above, because of the complicated interactions between TB medications and ART, these patients should be referred for urgent assessment by a specialist.

What about co-trimoxazole prophylaxis?

All PLWH who have active TB should receive co-trimoxazole throughout their TB treatment, as this has been shown to lower the risk of mortality.[4,6] Whether co-trimoxazole should be continued after TB treatment has ended will depend on the CD4 count—international or country specific guidelines should be referred to for further guidance.

CONCLUSIONS

As GPs are at the frontline of medical care, it is important for you to have an understanding of the multitude interactions between HIV and TB. The foundations to successful TB screening, prevention and treatment among PLWH are found in the recommendations enumerated in the STCI and WHO guidelines. For your patients that are PLWH who have not yet developed active TB, it is important to regularly screen for active TB and offer IPT for those that eligible. The institution of simple infection control measures in your clinics and hospitals can also protect your patients from acquiring TB infection. In patients that have developed active TB, minimizing diagnostic and treatment delays, testing for drug-resistant TB, using appropriate TB regimens, and initiating ART early on during TB treatment, can all greatly increase their chances of survival and relapse-free TB cure. Ideally, patients with TB and HIV co-infection should be managed by specialists.

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CIS CME–Questions

Management of HIV and Tuberculosis:
What Every GP Should Know

Questions

1 **Which of the following diagnostic tests is the recommended frontline test for PLWH suspected of having active, pulmonary TB?**

a. Smear microscopy
b. Interferon-gamma release assay (e.g. TB Gold)
c. Sputum culture
d. GeneXpert (Xpert MTB/RIF)

2 **You are seeing a 23 year old engineer who had sputum tested with GeneXpert, and the test result was "MTB detected, Rifampin resistance not detected." Which of the following statements is true:**

a. This patient does not need to be tested for HIV infection because he denies risk factors for HIV.
b. This patient should not be tested for HIV infection because he is not from a population where HIV prevalence is elevated
c. This patient should be tested for HIV infection because he has active tuberculosis

3 **You are seeing a patient in your clinic who was recently diagnosed with HIV. Which of the following is true about TB screening:**

a. This patient does not need to be screened for active TB
b. If the patient denies having a cough lasting more than 3 weeks, they do not need any further evaluation for active TB
c. To screen them for active TB, you should ask about the presence of the following symptoms: a cough of any duration, night sweats, fevers, and weight loss; if at least one of these is present they need further diagnostic evaluation for TB.
d. To screen them for active TB, you should obtain a CXR, even if they are asymptomatic; if any abnormality is present, further diagnostic evaluation for active TB is indicated.
e. Both c and d are correct.

4 **Which of the following interventions will lower the risk of active TB in PLWH?**

a. Antiretroviral therapy
b. Isoniazid preventive therapy
c. Co-trimoxazole
d. Both a and b are correct
e. a, b & c are correct

(Questions continued on the next page)

CIS CME–Questions

Management of HIV and Tuberculosis:
What Every GP Should Know
(Continued)

Questions

5 **Which of the following will lower the risk of mortality in PLWH who have active TB?**

a. Antiretroviral therapy initiation within 8 weeks of starting TB treatment
b. Isoniazid preventive therapy
c. Co-trimoxazole
d. Both a and c are correct
e. a, b & c are correct

6 **Which of the following is true about TB treatment regimens in PLWH?**

a. The preferred regimen is 2 months of isoniazid, rifampin, pyrazinamide and ethambutol, followed by 6 months of isoniazid and ethambutol; with treatment dosed intermittently (three times weekly) throughout
b. The preferred regimen is 2 months of isoniazid, rifampin, pyrazinamide and ethambutol, followed by 4 months of isoniazid and rifampin; with treatment dosed daily throughout
c. The preferred regimen is 2 months of isoniazid, rifampin, pyrazinamide and ethambutol, followed by 4 months of isoniazid and rifampin; with treatment dosed daily in the intensive phase and intermittently (three times weekly) in the continuation phase.

(See answers on the next page)

CIS CME–Answers

Management of HIV and Tuberculosis:
What Every GP Should Know
Questions on the previous two pages

Answers

1 **The correct answer is (d).** The WHO and STCI recommendation is that GeneXpert (Xpert MTB/RIF) be used as the frontline test for PLWH suspected of having active pulmonary TB. This test is more sensitive than sputum smear microscopy. The interferon-gamma release assay is a test for latent TB infection, it should not be used as a diagnostic test for investigating suspected active pulmonary TB. Sputum culture is highly sensitive and specific for the diagnosis of active pulmonary TB; however, GeneXpert is recommended as the frontline test because it provides results within a few hours, whereas sputum culture can take weeks.

2 **The correct answer is (c).** The WHO and STCI recommend that all persons diagnosed with active TB should be tested for HIV infection. This is because HIV is more common amongst persons with active TB, and also because the management of active TB will be different among patients that are PLWH.

3 **The correct answer is (e).** The WHO and the STCI recommend TB screening for PLWH in high TB burden areas. The WHO recommendation is to use symptom-based screening, and if resources are available, a CXR. The symptom-based screen recommended by the WHO consists of asking about the presence of four symptoms: fevers, coughs, night sweats, and weight loss; if any symptom is present, then active TB should be suspected and the patient will require additional diagnostic work up. A CXR should be used as a supplement to symptom-based screening to increase sensitivity. The CXR should be performed even amongst PLWH that do not have any of the four symptoms asked about in symptom-based screening; this will increase the sensitivity. The presence of any abnormality on a CXR means that further diagnostic testing (e.g., GeneXpert) should be pursued in order to diagnose or exclude active TB.

4 **The correct answer is (d).** Antiretroviral therapy and isoniazid preventive therapy both lower the risk of active TB in PLWH. All PLWH should be regularly assessed to determine if they meet criteria for initiating antiretrovirals.

5 **The correct answer is (d).** Antiretroviral therapy and co-trimoxazole lower mortality in PLWH who have active TB. Isoniazid preventive therapy is contraindicated when active TB is suspected (or confirmed, of course)—as this will expose the *M. tuberculosis* to isoniazid monotherapy which will lead to the development of isoniazid resistance. Antiretroviral therapy should be initiated in all PLWH who have active TB, regardless of their CD4 count, within 8 weeks of starting TB treatment.

(Answers continued on the next page)

Answers

6 **The correct answer is (b).** The preferred regimen for the treatment of active TB in PLWH is 2 months of isoniazid, rifampin, pyrazinamide and ethambutol, followed by 4 months of isoniazid and rifampin, with treatment dosed daily throughout. Regimens that used rifampin only in the intensive phase (question 6. choice "a.", where rifampin is used for only 2 months) have been associated with worse TB outcomes in PLWH (and also in HIV-uninfected TB patients). Intermittent TB therapy has also been associated with worse TB treatment outcomes in PLWH—hence, all efforts should be made to ensure PLWH who have active TB are treated with regimens in which dosing is daily throughout treatment.

Let's Talk TB

A Series on Tuberculosis, A Disease That Affects Over 2 Million Indians Every Year

Management of Drug-Resistant Tuberculosis: Q&A for Primary Care Physicians

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Abstract

Drug-resistant TB (DR-TB) is a serious and growing threat in India, especially in urban areas such as Mumbai. Multidrug-resistant TB (MDR-TB) is resistance to two of the most important first-line anti-TB drugs – isoniazid and rifampicin. Some patients develop more severe forms of DR-TB. Extensively drug-resistant TB (XDR-TB) is resistance to isoniazid and rifampicin, plus any fluoroquinolone, and at least one of 3 injectable second-line drugs (i.e., amikacin, kanamycin, or capreomycin). DR-TB occurs when patients fail to complete first-line drug therapy, have relapse, or newly acquire it from another person with DR-TB. If patients have any risk factors for drug-resistance, or live in a high MDR-TB prevalence area (e.g., Mumbai city), or do not respond to standard drug therapy, they must be investigated for MDR-TB using drug-susceptibility tests (DST) like GeneXpert, line probe assays, and liquid cultures. MDR-TB requires long-term and specialized treatment. So, patients should be referred to specialists, either in the private sector, or in the public sector where free MDR treatment is available. This Q&A covers commonly asked questions by the primary care doctor about identification and referral of patients with suspected or confirmed DR-TB.

Key words: tuberculosis; treatment; drug regimen; adherence, MDR-TB, XDR-TB

Q: WHAT IS MDR-TB AND WHY DOES IT MATTER?

MDR-TB is caused by TB bacteria that are resistant to at least isoniazid (INH) and rifampicin (RIF), the two most potent TB drugs in the standard, short-course TB treatment. According to WHO, India had an estimated 62,000 MDR-TB cases among notified pulmonary TB patients.[1] However, this number is likely to be an underestimate, as privately treated TB patients may not be notified.

Early diagnosis of MDR-TB is critical because the treatment regimen required is entirely different from standard, first-line anti-TB therapy (ATT). Treatment of MDR-TB is much longer (at least 2 years), more toxic, and very expensive. Even with correct management, mortality rates can approach 50%. Specialized care, therefore, is very important, and treatment must be guided by drug-susceptibility testing (DST) results.

Q: WHAT IS XDR-TB AND HOW COMMON IS IT?

XDR-TB is more severe resistance than MDR-TB. XDR-TB occurs when TB bacteria become resistance to INH and rifampicin, plus any fluoroquinolone (e.g., moxifloxacin or levofloxacin), and at least one of 3 injectable second-line drugs (i.e., amikacin, kanamycin, or capreomycin). Treatment of XDR-TB should never be done in primary care settings. Specialist treatment is mandatory. XDR-TB and pre-XDR TB increasingly seen in cities such as Mumbai, but are considered rare at the national level in India.[2-4]

Q: WHAT IS TOTALLY DRUG-RESISTANT TB (TDR-TB)?

Some hospitals, including in Mumbai, have reported a few cases where TB bacteria were found to be resistant to all of the drugs tested (first and second line).[3] Such resis-

tant strains have also been reported in other countries. While WHO does not recognize TDR-TB as a specific category, it is important to acknowledge the emergence of very extreme forms of DR-TB, where no drug therapy might work, and mortality rates are exceedingly high.

Q: WHEN SHOULD YOU SUSPECT DRUG-RESISTANT TB IN YOUR PATIENT?

DR-TB is more common in patients who:

- Do not take their TB medications regularly (i.e., in patients who are poorly adherent to ATT)
- Do not respond to standard ATT: they may be getting adequate treatment in the right doses during the intensive treatment, but show no clinical improvement. These patients may be persistently sputum AFB positive despite 2 months of adequately dosed drugs.
- Develop TB disease again, after having taken ATT in the past (i.e., in any patient with recurrence or relapse)
- Come from areas of India (e.g., Mumbai) where drug-resistant TB is widespread
- History of exposure to a patient with pulmonary DR- TB.

Q: IF YOU SUSPECT DR-TB IN YOUR PATIENT, HOW CAN YOU CONFIRM IT? WHAT ARE THE METHODS AVAILABLE FOR DRUG-SUSCEPTIBILITY TESTING (DST)?

The WHO recently announced the post-2015 "End TB Strategy".[5] A key component of this strategy is the push towards 'universal DST' which means that all TB patients should get a DST done at the time of their diagnosis. At the very least, all patients with history of previous TB treatment, treatment failure or recurrence, must undergo DST. In cities such as Mumbai, it is important to get a DST on ALL TB patients, regardless of risk factors.

DST can be done using two methods: genotypic and phenotypic. Genotypic methods are based on molecular tests that detect mutations in TB bacteria that confer drug-resistance. For example, mutations in the rpoB gene of *M. tuberculosis* is strongly associated with rifampicin resistance. Genotypic tests include Xpert MTB/RIF (GeneXpert), and Hain Genotype MTBDRplus and MTBDRsl(a commercial line probe assay). Phenotypic methods are based on detection of culture growth with and without TB drugs added to the culture media. Phenotypic methods include solid and liquid cultures. While solid cultures can take up to 2 months, liquid cultures (e.g., MGIT culture) can produce results within 2 weeks.

According to International Standards for TB Care (ISTC), DST should be performed at the start of therapy for all previously treated patients.[6] Patients who remain sputum smear-positive at completion of the intensive phase of treatment and patients in whom treatment has failed, have been lost to follow-up, or relapsed following one or more courses of treatment should always be assessed for drug resistance. For patients in whom drug resistance is considered to be likely, an Xpert MTB/RIF® test should be the initial diagnostic test, as per WHO policy.[6,7]Line-probe assay or liquid culture and DST to at least isoniazid and rifampicin should be performed promptly if rifampicin resistance is detected. If MDR-TB is detected, DST to second line TB drugs especially fluoroquinolones and injectable drugs is required for correct management. A rapid line probe assay called Genotype MTBDRsl for second-line drugs (i.e., fluoroquinolones and second-line injectable drugs) is now approved by WHO.

For DST, both WHO and ISTC recommend Xpert MTB/RIF® test as the initial diagnostic test because it can rapidly detect rifampicin resistance within 90 minutes with high accuracy, and allow clinicians to initiate empiric MDR therapy, pending confirmation with cultures.[7] Hence in areas (e.g., Mumbai) where levels of primary drug resistance are high, it is imperative to send out the sputum (in pulmonary TB) and/or other samples from appropriate sites (in extra-pulmonary TB) for an Xpert MTB/RIF test.

Line-probe assays (e.g., Hain Genotype MTBDRplus and MTBDRsl) or liquid culture and DST should then be performed promptly if rifampicin resistance is detected using Xpert MTB/RIF. Once culture and DST results are obtained, MDR therapy can be customized to the patient's drug-susceptibility profile, and must include a combination of at least 5 drugs to which the TB bacilli are still sensitive. The algorithm for DST is shown in the graphic (**on the next page**).

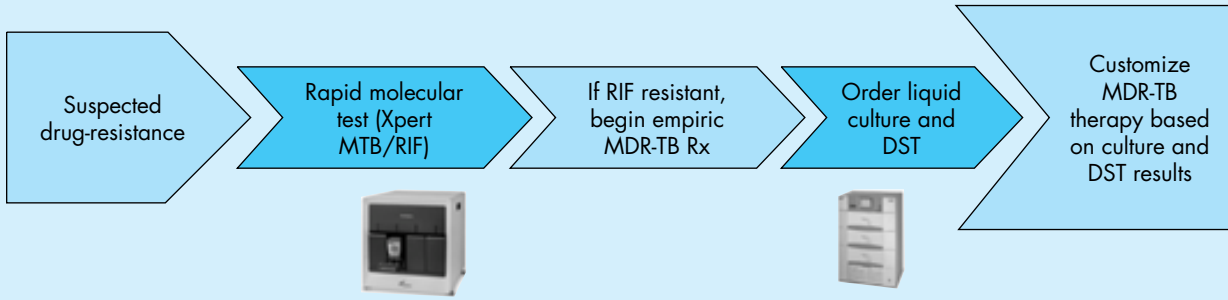
Q: IS IT IMPORTANT TO ALWAYS SEND A SAMPLE FOR MGIT CULTURE?

Yes, especially if you are suspecting MDR-TB in your patient, or practising in an area of high prevalence of MDR-TB. The liquid culture is the gold standard for the diagnosis of TB, and MDR-TB. Every other test is compared against the liquid culture. Since culture results can take a few weeks, it is important to send out cultures early on in the treatment for the following reasons:

- It is the gold standard for the confirmation of TB itself.
- Both pulmonary and extra-pulmonary samples can be subjected to culture
- Culture confirms the diagnosis of TB as opposed to atypical mycobacteria or nocardiosis (smear microscopy may still be positive in the latter two)
- A positive culture can be subjected to a line probe assay for an early diagnosis of MDR-TB.
- Cultures are the only tests that assay a variety of first and second line drugs, and confirm MDR and XDR-TB.

When you practice in a high-prevalence area of TB,

Algorithm for Drug-Susceptibility Testing (DST)



you will save a lot of time for the patient by sending out cultures early on in the treatment. In a scenario where the patient turns out to have drug-sensitive strains on a culture, you can rest assured you are on the right track, and the money spent on culture and first-line DSTs was worth it. If the patient turns out drug-resistant, then you have saved an enormous amount of time of the patient on diagnosis, and appropriate individualised treatment by the concerned specialist.

Q: WHEN SHOULD YOU REFER THE PATIENT TO A SPECIALIST?

- To confirm the diagnosis of TB, if in doubt
- To obtain invasive samples for testing (e.g., bronchoalveolar lavage, or pleural biopsy)
- To get a treatment plan, if the patient has co-morbidities like diabetes, immunosuppressive conditions, etc. Remember diabetes triples the risk of developing TB, and increase the severity of TB too. Conversely TB can worsen blood glucose control as well, in patients with TB.
- To decide on addition of steroids to an ATT regimen
- If adverse effects are unmanageable at primary care level
- If drug-resistant TB is confirmed (through molecular or culture tests), for a management and monitoring plan
- If lung resection surgery is indicated for any reason, be it for the diagnosis or treatment of the tuberculosis.

Patients can be referred to specialists in either the private/public sector. The Revised National TB Control Program (RNTCP) in India is steadily increasing its capacity to offer MDR-TB therapy via Programmatic Management of Drug-resistant TB (PMDT) centers and hospitals, where free MDR-TB therapy is available. This is a useful option for patients unable to afford private care.

Q: WHAT ARE THE COMMONEST MANAGEMENT ERRORS THAT CAN RESULT IN ACQUIRED DRUG-RESISTANCE?

- Addition of a single drug to a failing regimen. Many physicians add a quinolone to the 4 first-line drugs (HRZE) when the standard therapy does not result in improvement. This is wrong, and believed to be one of the causes of high fluoroquinolone resistance in MDR-TB of late.
- Prescribing only 2 or 3 drugs in the intensive phase. The intensive phase should always have 4 drugs. Otherwise, the bacteria mutate and develop resistance.
- Prescription of second-line drugs in the first instance. Some physicians have the mistaken perception that second-line drugs are more potent than first-line medication. In fact they are less effective (and more toxic) drugs, and should be reserved only for patients with DR-TB, or first-line drug intolerance.
- Prescribing total drugs for an inadequate duration – e.g., 2 to 4 months, instead of the minimum of 6 months.
- Under-dosing of first-line medication is another common problem – many physicians prescribe drug 'kits' or fixed dose combinations (FDCs), in the belief that everyone falls in a fixed weight category. This is obviously not the case. A significant number of patients with TB are significantly underweight and overweight too, and this needs appropriate adjustment of dosing.
- Sometimes, patient switch between doctors, and if the new doctor changes the regimen without adequate drug-susceptibility information, then this might result in inappropriate regimens that increase risk of resistance.
- Patients may feel better and decide to stop taking medications. Premature stoppage occurs, with disastrous consequences on cure, and of course increased risk of drug-resistant bacilli.
- Drug-related side effects (if not adequately counselled on at the outset) is another common reason for non-adherence, and possible treatment default.
- Stigma of the disease and sometimes cost (though not very high for first-line drugs) has been a reason for non-adherence and treatment default in the past.
- Finally, personal/social issues like village travel, death in the family etc. have also been reasons for patients in-

terrupting their treatment at crucial stages (especially intensive phase), with resultant disastrous consequences.

Q. IS IT PROPER TO TREAT MDR-TB (ONCE CONFIRMED) IN GENERAL PRACTICE?

No, this is not advisable for the following reasons:

- MDR and XDR-TB do not have a simple, standardised treatment plan. Drug therapy needs to be customized to the individual patient's DST profile.
- The cost and duration of treatment are significant, and need to be appropriately counselled on.
- The side effects of the various drugs are significant and common, and often difficult to manage. Hospitalization may be required to manage severe cases.
- A significant number of patients default on treatment, spreading the disease further. Hence significant time needs to be spent with the patient, something not easy in a primary care practice.
- A lot of treatment is based on experience of the specialist and his ability to counsel patients and their care-givers appropriately. Early detection and treatment of XDR is also very critical here.
- Finally, a significant number of patients may benefit with surgery in MDR-TB. Examples include decortications, lobectomy and pneumonectomy. Decisions regarding this should be taken by a respiratory physician early in the treatment course, in consultation with an experienced thoracic surgeon. These are decisions beyond the purview of primary care.

Q. IS IT PROPER TO MONITOR MDR-TB TREATMENT IN PRIMARY CARE?

Absolutely, yes. Every patient trusts his or her GP the most, and especially if the GP is competent to manage drug-sensitive TB well, and alert to refer to a specialist when required. These qualities in a GP increase trust by the patient. The patient with MDR-TB will always need a primary care physician to monitor her disease, especially sputum cultures when appropriate, drug-related side effects, communication with the specialist on need for interval bronchoscopies (to ascertain culture status in lung MDR-TB), and decisions on major surgery. Your patient will value your role here.

Q. IN THE ABOVE CONTEXT, WHAT ARE THE SECOND-LINE DRUGS FOR TB AND THEIR SIDE EFFECTS?

Group 1 are the first-line drugs: isoniazid, rifampicin, ethambutol, pyrazinamide

Group 2

Aminoglycosides: (any one drug to be used) Streptomycin, Kanamycin, Amikacin, Capreomycin

- 15 mg/kg/day
- Monitor creatinine, vestibular and ototoxicity
- Check for giddiness, Romberg's sign, tinnitus or reduced hearing as early signs of ototoxicity
- Most MDR-TB patients are streptomycin resistant too, so avoid using streptomycin in an empiric MDR regimen
- Kanamycin and Amikacin exhibit some cross-resistance
- Capreomycin exhibits no cross-resistance
- Patients who are unable to take regular intramuscular injections (up to 6 months at least), may need to take intravenous amikacin through a PICC line

Group 3

Fluoroquinolones (ofloxacin, levofloxacin and moxifloxacin) – any one to be used

- Usually cross-resistant to each other, except for moxifloxacin which can still exhibit activity despite resistance to other fluoroquinolones
- Giddiness, headache and GI upsets are the commonest side effects
- Teratogenic effects
- Concern in small children with growing cartilage

Group 4 – less potent oral agents

Thioamides (ethionamide and prothionamide)

- 15 – 20 mg/kg/day (max 1 gm/day)
- Epigastric discomfort – hence start with 250 mg twice daily initially and then increase the dose if tolerated.
- Hypothyroidism
- Hypoglycaemia
- Teratogenic effects
- Cross-resistance between drugs

Cyloserine and Terizidone

- 10- 20 mg/kg/day
- Altered behaviour, mood swings, suicidal tendencies
- Giddiness, seizures
- Avoid in alcoholics, epileptics and mental illness
- Slurred speech

Para-aminosalicylic acid (PAS)

- 150mg/kg/day in 2 divided doses
- GI upsets
- Avoid the sodium salt in patients needing salt restriction
- Hypothyroidism

Group 5 – Drugs for whom anti-tuberculosis action has not been documented in clinical trials

- Thioacetazone
- Clofazimine
- Linezolid
- Amoxycillin-clavulanic acid
- Clarithromycin
- Imipenam – cilastatin
- High dose isoniazid

New TB drugs for MDR-TB that are not approved for clinical use in India

Two new drugs are now available for TB: bedaquiline and delamanid. Clinical trials on these drugs are ongoing and approval by the Indian regulatory agency is expected in future. Currently, these drugs should

NOT be used by primary care providers. They might be available for specialist use on compassionate grounds.

Bedaquiline:

- SIRTURO® by Janssen Therapeutics ™ (bedaquiline; https://www.sirturo.com/) is a diarylquinoline antimycobacterial drug indicated as part of combination therapy in adults (≥18 years) with pulmonary multi-drug resistant tuberculosis (MDR-TB).
- SIRTURO was the first new TB drug with a novel mechanism of action to be made available for more than 40 years and was granted accelerated approval by the United States FDA. It is still in Phase III trials.
- SIRTURO is restricted for use only when an effective treatment regimen cannot otherwise be provided.

Delamanid:

- Delamanid (also known by its trade name, Deltyba® by Otsuka Pharmaceutical Co., Ltd) is a drug in the nitroimidazole class.
- Delamanid is a new potential option for people with MDR-TB who lack effective, tolerable treatments.
- Delamanid was granted conditional approval by the European Medicine Agency in April 2014. Information about this new drug is limited, since it has only been through Phase IIb trial and studies for safety and efficacy.

Interim policy guidance on these new drugs is available from WHO.[8]

Q: WHAT ARE THE THINGS TO REMEMBER WHEN CHECKING THE PRESCRIPTION OF A SPECIALIST FOR MDR-TB?

- As a GP, your role is paramount. A good primary care physician can be alert to wrong prescriptions and remind a specialist at times, that the direction or plan of treatment is wrong. Remember you see the patient far more frequently than the specialist.
- Check that at least 4 new drugs have been commenced, preferably one from Group 2 and 3, and 2 more, from **Group 3, 4** or **both** (depending on whether the patient has MDR, XDR or TDR TB)
- Check that none of the drugs are contra-indicated for your patient:

- Hearing loss pre-existing	- Chronic kidney disease
- Mental illness	- Pre-existing seizure disorder
- Visual disturbances	- Pre-existing sever gastritis

- Do a skin sensitivity test before administering the aminoglycoside the first time.
- A drug that was used within a previous failing regimen should never be used again if possible, and should not be counted in the total of 4 drugs for re-treatment.
- Monitor CBC and platelets in patient on linezolid
- Monitor for visual disturbances in patient on linezolid.

Q: QUESTIONS YOU NEED TO ASK THE SPECIALIST PERIODICALLY DURING THE TREATMENT OF MDR-TB?

- Is the patient non-infectious?
- When do you next need a sputum/bronchoscopic sample for AFB culture?
- When should the next round of chest x-rays be done?
- Is a CT scan chest indicated, and if so, for what purpose?
- If there is a persistent cavity despite clinical improvement, how can we ensure the patient is still not harbouring active infection? (usually a bronchoscopic aspirate is indicated here)
- What is the likely total cost of treatment, excluding any surgery?
- Is the patient a candidate for surgery, and if so what is the likely cost?
- How long do you expect the entire duration of treatment to last?

It is very important to ask these questions, since the same message (specialist's) needs to be constantly reinforced by the primary care physician as well, to ensure better adherence at all stages of treatment.

All in all, remember that treating and supervising MDR-TB management in clinical practice is a big responsibility and needs commitment and time. If you are unable to manage the same, refer to an appropriate specialist. Never feel you will lose your patient that way. Your role to monitor for side effects is paramount; so too your role in ensuring adherence. Patients are ever-grateful when they are referred to the right specialists. Their confidence in you (as their primary care physician) will only increase. ■

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Let's Talk TB

A Series on Tuberculosis, A Disease That Affects Over 2 Million Indians Every Year

Childhood Tuberculosis: Q&A for Primary Care Physicians

Madhukar Pai, MD, PhD—Author and Series Editor

Abstract

GPs frequently see children in their clinical practice, and should be alert to the possibility of pediatric TB, especially in malnourished children. Children with TB often present with vague, non-specific symptoms, and this makes it hard to suspect and diagnose TB. Symptoms could include chronic fever, cough, weight loss, fatigue, loss of appetite, failure to gain weight, and lymph node enlargement. History of contact with an adult with TB is therefore a very important component of history that should be elicited. There is no adequate gold standard test for childhood TB, and diagnosis requires multiple tests. Smears for acid-fast bacilli (AFB) are often negative because of the low numbers of AFB in childhood TB. Therefore, liquid culture and molecular tests (Xpert MTB/RIF) will be most helpful, along with signs, symptoms, chest radiology, evidence of TB infection (e.g. positive Mantoux skin test), and history of contact with active TB. All children who have not been treated previously and do not have other risk factors for drug resistance should receive a WHO-approved first-line treatment regimen for a total of 6 months. The initial phase should consist of two months of isoniazid, rifampicin, pyrazinamide and ethambutol. The continuation phase should consist of isoniazid and rifampicin given for 4 months. Daily treatment is preferable to intermittent therapy. Drug dosages are calculated according to weight (not age). Adherence to the full course of anti-TB therapy is very important to ensure high cure rates. In general, children tolerate first-line anti-TB therapy very well with low risk of toxicity.

Key words: childhood tuberculosis; diagnosis; treatment

Q: WHAT IS CHILDHOOD TB AND WHO IS AT RISK?

India has the largest number of TB cases. GPs frequently see children in their clinical practice, and should be alert to the possibility of pediatric TB. It is estimated by WHO that there are more than half a million cases of TB in children occurring globally each year. Children usually get infected because of adults in the family with active TB. In low and middle income countries, TB is an important cause of morbidity and mortality in children.

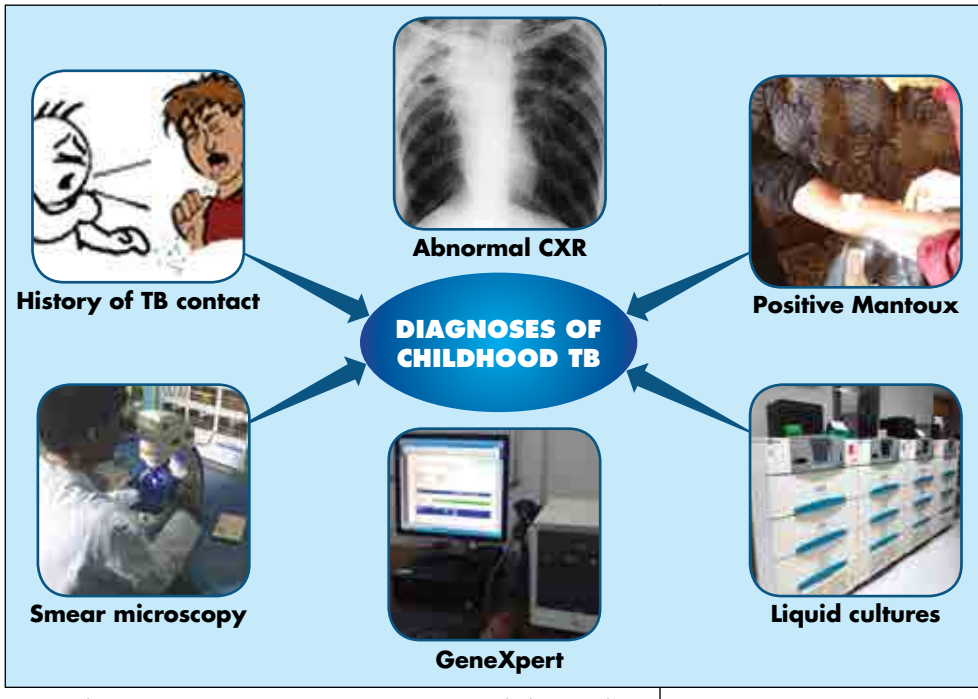
TB in children is difficult to diagnose, and easy to miss. Young children can develop extrapulmonary and severe forms of TB such as TB meningitis and miliary TB, and thus children are a vulnerable population. TB in children can result in malnutrition, while malnutrition itself is a major risk factor for development of TB in children. HIV-infected children are also at high risk of developing TB. In India, malnutrition in children is easily the biggest risk factor for childhood TB, given the high prevalence of under-nutrition in children.[1]

Q: CAN WE PREVENT TB IN CHILDREN?

BCG vaccination at birth is routinely done in many countries including India, and it does have an important role, especially in reducing the risk of severe, disseminated (i.e. miliary) disease in young children that are infected with TB. However, the protective efficacy of BCG is low, and a BCG-vaccinated child cannot be considered to be protected from TB. Multiple does of BCG is not recommended as there is no evidence of increased protection by giving repeat vaccinations.

Q: WHEN SHOULD WE SUSPECT TB IN A CHILD?

Children with TB often pres-



ent with vague, non-specific symptoms, and this makes it hard to suspect and diagnose TB. Symptoms could include chronic fever, cough, weight loss, fatigue, loss of appetite, failure to gain weight, and lymph node enlargement. History of contact with an adult with TB is therefore a very important component of history that should be elicited. If an adult in the family has drug-resistant TB (e.g., MDR-TB), this is critical to know.

Q: HOW IS CHILDHOOD TB DIAGNOSED?

No single test works well in childhood TB. So, the diagnosis of TB in children usually relies on a combination of clinical features, and laboratory tests (see box above). The following clinical history and tests should be done:

- History of contact with an adult with TB disease
- Any symptom suggestive of TB (see above)
- Mantoux (tuberculin) skin test or an interferon-gamma release assay: a positive test provides evidence of TB infection
- Chest X-ray (which can show hilar adenopathy)
- Microbiological tests of sputum or other clinical samples (e.g. gastric juice):

-Smear microscopy (AFB)
-Xpert MTB/RIF (GeneXpert)
-Liquid cultures

A combination of the above can help detect childhood TB. Sometimes, when the above combination fails to detect TB, it may be necessary to empirically treat for TB and assess the clinical response.

Q: WHAT CLINICAL SAMPLES SHOULD BE SENT FOR TB TESTING?

While young children are unable to produce sputum, sputum could be collected from older children and adolescents. At least two sputum specimens must submitted for microscopic examination and Xpert MTB/RIF testing and culture. In young children (<7-8 years of age), the routine specimens collected are two to three fasting gastric aspirates (gastric juice aspirate). However, the collection of 2-3 fasting, early morning gastric aspirate specimens is cumbersome and usually requires hospitalization. The following are basic guidelines for collecting gastric aspirates: 1) Specimens are collected after the child has fasted for eight to ten hours and, preferably, while the child is still in bed; 2) Specimens are usually collected daily for three days.

Extrapulmonary TB can occur in many sites, the most common sites being lymph nodes and meningeal. EPTB cannot be diagnosed with sputum or blood specimens. It is critical to make an effort to collect tissue and fluids from the site of the disease. This may require surgical expertise and referral to a center where biopsies can be done safely. For example, if TB meningitis is suspected in a child, then it is important to refer the child to a hospital where lumbar puncture can be performed for CSF testing.

Q: HOW ACCURATE IS XPERT MTB/RIF (GENEXPERT) IN CHILDREN?

Pooled data from several studies show that compared with culture, the sensitivities and specificities of Xpert for tuberculosis detection is 62% and 98%, respectively, with use of expectorated or induced sputum samples and 66% and 98%, respectively, with use of samples from gastric aspirate.[2] Xpert sensitivity is about 36-44% higher than sensitivity for smear microscopy. Xpert's sensitivity and specificity to detect rifampicin resistance is 86% and 98%, respectively. Thus, Xpert is superior to smear microscopy, and should be routinely used in children, where available. The fact that Xpert performs well

in gastric juice samples is worth underscoring, as gastric aspirates may be easier to collect from young children than sputum samples.

Q: CAN XPERT MTB/RIF (GENEXPERT) BE USED FOR EXTRAPULMONARY TB DIAGNOSIS IN CHILDREN?

Yes, WHO has recommended the use of Xpert MTB/RIF in two extrapulmonary samples: lymph node tissues, and CSF samples. In CSF samples, Xpert has a sensitivity of about 81% and specificity of 98%.[3] In lymph node tissues, Xpert has a sensitivity of about 83% and specificity of 94%.[3]

Q: CAN CHILDREN HAVE DRUG-RESISTANT TB? HOW CAN MDR-TB BE DIAGNOSED IN CHILDREN?

Yes, children in contact with adults with MDR-TB can become infected with drug-resistant strains, and develop MDR-TB. Drug-resistant TB should be suspected in any child that is receiving TB treatment and not improving. Diagnosis of MDR-TB can be achieved by using rapid molecular tests such as Xpert MTB/RIF, and line probe assays (e.g., Hain Genotype MTBDRplus). Liquid cultures can also be used to detect drug resistance. Sputum, gastric aspirate and extrapulmonary samples can be subjected to Xpert, and liquid cultures and DST. Children with suspected or confirmed drug-resistant TB should be referred to a specialist – for additional investigation and specialist management.

Q: ONCE TB IS DIAGNOSED, WHAT IS THE RECOMMENDED TREATMENT IN CHILDREN?

All children who have not been treated previously and do not have other risk factors for drug resistance should receive a WHO-approved first-line treatment regimen for a total of 6 months. The initial phase should consist of two months of isoniazid, rifampicin, pyrazinamide and ethambutol. The continuation phase should consist of isoniazid and rifampicin given for 4 months. Daily treatment is preferable to intermittent therapy. Drug dosages are calculated according to weight (not age). **Table** shows the recommended drug dosages in children.[4]

Table 1– Doses of first-line antituberculosis drugs in children

Drug	Recommended dose in mg/kg body weight (range)
Isoniazid	10 (7-15)
Rifampicin	15 (10-20)
Pyrazinamide	35 (30-40)
Ethambutol	20 (15-25)

Source: Reference 4

Adherence to the full course of anti-TB therapy is very important to ensure high cure rates and to prevent the emergence of drug-resistance. Children with malnutrition should receive adequate nutritional rehabilitation therapy, along with anti-TB treatment. Severely malnourished children with TB may require hospitalization and careful monitoring.

Q: HOW CAN WE MONITOR TREATMENT IN CHILDREN AND WHAT ARE THE LIKELY ADVERSE EFFECTS?

Resolution of symptoms and weight gain are markers of a satisfactory treatment response in sputum smear-negative cases. If a child has smear-positive TB, then it is important to check if the smears become negative at the end of the intensive treatment phase. Xpert MTB/RIF is not recommended for treatment monitoring.

Children tolerate first-line anti-TB therapy very well with low risk of toxicity. Adherence can be a challenge especially during the continuation phase. So, it is important to counsel the parents and the family about importance of completion of full course of anti-TB treatment.

Comprehensive information on childhood TB is available from WHO and IUATLD in the Childhood TB Training Toolkit published in 2014.[5]

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Let's Talk TB

A Series on Tuberculosis, A Disease That Affects Over 2 Million Indians Every Year

Management of Tuberculosis: 10 Common Pitfalls to Avoid

Srinath Satyanarayana, MD—Co-author
Madhukar Pai, MD, PhD—Author and Series Editor

Abstract

Indian TB patients get diagnosed after a delay of nearly two months, and are seen by 3 different providers before a diagnosis is made. At the primary care level, patients rarely get investigated for TB, even when they present with classic TB symptoms. Instead, providers give broad-spectrum antibiotics (e.g., fluoroquinolones) and remedies such as cough syrups and steroids. Even when TB is considered likely, private physicians tend to order tests that are non-specific, such as complete blood count, ESR, Mantoux test, and chest X-rays. They rarely seek microbiological confirmation via sputum smear microscopy, culture or polymerase chain reaction tests. Even if the diagnostic hurdle is overcome, TB treatment in the private sector is far from standard. When private practitioners initiate anti-TB treatment, they tend to use drug regimens that are not recommended by WHO or the International Standards of TB Care. Furthermore, private practitioners often fail to ensure treatment completion, and provide adherence support to their patients. This article discusses the 10 most common pitfalls that doctors should avoid. Addressing these pitfalls should great improve the quality of TB care in India.

Key words: tuberculosis, common pitfalls, management errors

PITFALL 1: NOT RECOGNIZING AND SUSPECTING TB

Doctors in India often miss TB, because they do not suspect TB in patients presenting with cough for 2 weeks or longer.[1] Multiple rounds of broad-spectrum antibiotics are tried, but tests for TB are rarely ordered at the primary care level.[2] Even when TB is suspected, history taking is often incomplete – family history of TB is rarely elicited, and previous treatment for TB is also missed.[2]

PITFALL 2: INADEQUATE DIAGNOSTIC WORK-UP

When doctors in India think of TB, they often order non-specific tests such as total and differential blood counts (TC/DC), erythrocyte sedimentation rate (ESR), and chest X-ray.[1,2] While these tests can be helpful, they do not confirm tuberculosis. Abnormal X-rays, for example, do suggest TB, but other lung conditions can also produce abnormalities on radiography. So, only relying on chest x-ray can result in over-diagnosis. Tuberculosis can only be confirmed by microbiological tests such as sputum smear microscopy, GeneXpert, and cultures. So, it is very important to order sputum tests that can directly detect *Mycobacterium tuberculosis*.

PITFALL 3: USE OF INAPPROPRIATE DIAGNOSTIC TESTS

Active tuberculosis is a microbiological diagnosis. Serological, antibody-based tests (e.g., TB ELISA) are inaccurate and banned by the Indian government.[3] They should not be used for TB diagnosis. In India, there is growing concern that tests such as Mantoux (tuberculin skin test) and IGRAs (e.g., TB Gold, TB Platinum) are being misused for active TB diagnosis. These tests were designed to detect latent infection, and cannot separate latency from active disease.

The Standards for TB Care in India (STCI) clearly states that both TST and IGRAs should not be used for the diagnosis of active TB in high endemic settings like India.[3] If Man-

toux and IGRAs are used for active TB diagnosis, this will result in significant over-diagnosis of TB, because of the high background prevalence of latent TB infection in India. In children, STCI suggests that the Mantoux test may have some value as a test for infection, in addition to chest x-rays, symptoms, history of contact, and other microbiological investigations (e.g., gastric juice acid fast bacilli and Xpert MTB/RIF).[3]

PITFALL 4: NOT CONSIDERING THE POSSIBILITY OF DRUG-RESISTANT TB (DR-TB)

DR-TB occurs when patients fail to complete first-line drug therapy, have relapse, or newly acquire it from another person with DR-TB. All persons who have previously received TB therapy must be considered to have suspected DR-TB. If patients have any risk factors for drug-resistance, or live in a high MDR-TB prevalence area (e.g., Mumbai city), or do not respond to standard drug therapy, they must be investigated for MDR-TB using drug-susceptibility tests (DST) like GeneXpert, line probe assays, and liquid cultures. Indian physicians under-use DST and this can result in mismanagement.

PITFALL 5: EMPIRICAL MANAGEMENT OF SUSPECTED TB WITH QUINOLONES AND STEROIDS

When doctors suspect TB or other lower respiratory tract infections, they frequently use broad-spectrum fluoroquinolones (e.g., levofloxacin, moxifloxacin) for short periods. However, such empirical management with fluoroquinolones will mask and delay the diagnosis of TB. Fluoroquinolones, in particular, are bactericidal for *M. tuberculosis* complex. Empiric fluoroquinolone monotherapy for respiratory tract infections has been associated with delays in initiation of appropriate anti-tuberculosis therapy and acquired resistance to the fluoroquinolones.[4] Doctors also tend to use steroids in individuals with history of chronic cough. Steroids, again, can result in temporary clinical improvement, but delay the diagnosis and treatment of underlying tuberculosis.

PITFALL 6: ONCE TB IS DIAGNOSED, NOT ADDRESSING CO-MORBIDITIES AND CONTACTS

Once TB is diagnosed, it is important to make sure the patient is not suffering from co-morbid conditions such as HIV and diabetes. It is also important to check if the patient is a smoker/alcoholic and provide them advice on smoking/alcohol cessation. It is also necessary to ask about TB symptoms among family members. In particular, small children living in the same family as the adult case must be tested for TB.

PITFALL 7: USE OF IRRATIONAL TB DRUG REGIMENS

Even if the diagnostic hurdle is overcome, TB treatment in the private sector is far from standard.[1] When private practitioners initiate anti-TB treatment (ATT), they tend to use drug regimens that are not recommended by WHO or the Standards of TB Care in India (STCI). All patients who have not been treated previously and do not have other risk factors for drug resistance should receive a WHO-approved first-line treatment regimen for a total of 6 months.[4] The initial phase should consist of two months of isoniazid, rifampicin, pyrazinamide and ethambutol. The continuation phase should consist of isoniazid and rifampicin given for 4 months.

There is no need to add additional drugs such as quinolones to the standard drug regimen.[4] Also, there is no need to extend the duration of treatment beyond 6 months, unless there is evidence of treatment failure, or there are complications (e.g., bone & joint TB, spinal TB with neurological involvement and neuro-tuberculosis). Drug dosages should be based on body weight, and daily dosing is preferable.[4] Some physicians have the mistaken perception that second-line medication are more potent than first-line medication. In fact they are less effective (and more toxic) medications, and should be reserved only for patients with drug-resistant TB, or first-line drug intolerance.

PITFALL 8: NOT ENSURING TREATMENT ADHERENCE

Adherence to the full course of ATT is critically important to ensure high cure rates and to prevent the emergence of drug-resistance. But private practitioners struggle to ensure adherence. Most do not maintain any medical records, and this makes it very difficult to follow-up patients. Patients often do not receive sufficient counseling about the importance of completing the full course of ATT. Drug-related side effects (if not adequately counselled on at the outset) is another common reason for non-adherence, and possible treatment default.

Every TB patient should receive counseling at the start of TB treatment. By notifying all TB cases to the local health authorities, private practitioners can seek help from the public sector to help follow-up patients who default. Physicians can also work with community-based organizations, and enlist community health workers to supervise treatment.

PITFALL 9: NOT MONITORING RESPONSE TO THERAPY AND CHANGING REGIMENS WITHOUT DST

Once ATT is started, doctors have the responsibility

of monitoring the patients to check whether therapy is working. This requires follow-up smear and culture testing. Negative smears at the end of therapy is important to ensure cure. If a patient is not responding to ATT, it important to investigate why. Addition of a single drug to a failing regimen is a big concern. Many physicians add a quinolone to the 4 first-line drugs (HRZE) when the standard therapy does not result in improvement. This is wrong, and can result in MDR-TB.

Sometimes, patients end up moving from one doctor to another, and each time the drug regimen gets modified without adequate drug-susceptibility testing (DST) to guide the choice of drug combinations. This creates a perfect environment for drug-resistance to emerge or worsen.

PITFALL 10: NOT NOTIFYING ALL CASES AND USING FREE PUBLIC SECTOR SERVICES FOR VULNERABLE PATIENTS

TB treatment is available free of cost to all patients in India via the Revised National TB Control Programme (RNTCP).[5] So, private practitioners can refer all TB patients for treatment through the RNTCP, unless patients insist on being treated in the private sector. RNTCP provides a range of services such as contact investigation, linkage to free TB drug programs, adherence support, and linkage to PMDT services for patients with MDR-TB.[5] By availing these free services, patients can protect themselves from catastrophic health expenditures. Irrespective of where the patients are diagnosed and treated, it is mandatory for private practitioners to notify all TB cases to their respective District or Corporation TB Officers.

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What Counselling and Support Do Patients With Tuberculosis Need?

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Abstract

Persons affected by tuberculosis and their family members should be counselled at every opportunity, to address information gaps and to enable informed decision-making. Counselling should also address issues such as healthcare, physical, financial, psycho-social and nutritional needs. The objective of counselling is to meet the needs and ensure the rights of the patient. The objective is also to support the patient where possible to overcome barriers to successful treatment. During counselling, patients need to be informed about TB, how the disease spreads, signs and symptoms, consequences of not following treatment guidelines, why treatment is long and why completion of treatment is critical, likely adverse events during therapy, and cost involved in treatment and what free/public services are available to patients. Patients need to be told that TB is a fully curable and treatable disease. We must use patient centred approaches, and recognize that all TB patients deserve a minimum package of holistic TB care services that are not restricted to diagnosis and pharmacological treatment, but include counselling and support services as well.

Key words: tuberculosis, counselling, patient support, patient-centric care

WHY IS COUNSELLING IMPORTANT?

Have you ever walked into your GP's clinic, waited in line for 30 minutes, spent about 5 minutes with your doctor and left with a prescription in hand? Unfortunately, due to the extremely busy schedules of our GPs, the average consultation time lasts barely a few minutes and during this time, very few questions are asked of the patient.[1,2] A crucial step missing in this process is that of 'patient counselling'. In India, the patient-provider relationship is often one where there is unparalleled respect for the physician; the patient often has blind faith in their diagnosis and subsequent treatment guidelines. Due to this asymmetric relationship and rushed consultation, patients do not always receive the adequate education and counselling they deserve.

Patient education is defined as follows: Education to help patients and their families understand the disease and treatment, cooperate with healthcare providers, live healthily, and maintain or improve their quality of life.[3] In the case of a disease such as tuberculosis (TB), patient education along with appropriate counselling i.e., enabling them to cope with the stress and take personal decisions related to the disease, is the need of the hour. TB in India is plagued by a number of challenges; some of these are related to the patient's inaccurate or incomplete knowledge, incorrect behaviour beliefs and stigma-generating attitudes. Patient counselling can therefore play a crucial to counter these problems.

The Revised National Tuberculosis Programme (RNTCP) of the Ministry of Health and Family Welfare (MoHFW) also recognizes the urgent need to scale up counselling and psychosocial support services for patients.[4] India's ambitious National Strategic Plan (NSP) for TB prevention and control (2012 – 2017) highlights that patient counselling through a professional counsellor is a missing link in the programme. It attributes counselling to be a critical intervention that can enhance treat-

Standards for TB Care in India[6] (STCI) states:

Standard 26: Addressing counselling and other needs

Persons affected by TB and their family members should be counselled at every opportunity, to address information gaps and to enable informed decision-making. Counselling should also address issues such as healthcare, physical, financial, psycho-social and nutritional needs.

ment adherence and improve treatment outcomes.[5]

CHALLENGES FACED BY TB PATIENTS

The journey of a TB patient from the time of the onset of symptoms to treatment completion is not an easy one. Many of the factors that increase a person's vulnerability to TB or reduce their access to services to prevent, diagnose and treat TB are associated with their ability to realize their human rights.

A former TB patient herself, Deepti Chavan Musale highlights that, 'a TB patient has to deal with a lot of things including the side effects of the medicines, stigma, discrimination etc. Additionally the duration of treatment is very long and fighting TB is not only a physical battle but one that requires you to be very strong mentally too.'

In the case of TB, adherence to treatment is vital. Inability to comply can lead to advanced stages of TB, such as multi drug resistant (MDR) TB. TB drugs come with a host of side-effects and counselling helps patients become aware of the effects that they might face and the importance of compliance. Some of the side effects to commonly used TB drugs may include feeling sick or dizzy, skin rashes, pins and needles and flu like symptoms which become worse (e.g., jaundice) in the case of second line TB drugs used to cure MDR TB.[7]

Along with the potential of infecting families and communities, there is a deep-rooted stigma attached to a TB patient, which often prevents them from accessing services. Any gap in timely and accurate diagnosis and treatment perpetuates TB transmission, despite the widespread availability of effective and inexpensive treatment. The principal effects of stigma in developing countries are social isolation of patients, both outside the family, where the person may be avoided by former friends and acquaintances and inside the family where the patient may be forced to eat and sleep separately.[8]

Patient and family counselling plays an important role in addressing the above issues and also plays a role in helping patients deal with the financial burden and nutritional barriers to cure TB successfully.

PATIENT COUNSELLING AND SUPPORT: WHEN AND HOW

Psychological distress such as depression and other mental co-morbidities have often been associated with TB,[9] with rates of mental illness reaching as high as 70% among TB patients.[10] Resulting chronic stress can impact a TB patient, firstly by impairing his or her immune system,[11] and secondly (and more specifically) affect his or her ability to adhere to treatment.[12] With challenges related to adherence to TB treatment resulting in a number of undesirable consequences, it is important to understand the contributing factors and the role for counselling. A critical review by Sabaté describes these as five interacting factors, i.e., socio-economic, health system, condition related, therapy related, and patient related.[13] Counselling, which can take on the form of simple information sharing or more specialized services directed toward improving outcome expectations for the illness and encouraging patient self-efficacy and motivation to achieve a complete cure, can be used to address some of these contributing factors.

There are a number of toolkits[14,15,16,17] that have been created to train counsellors for patient counselling. It is however important for the physician to also understand and value this component of TB care. Broadly summarizing the wealth of information cited, it is important to remember:

- The objectives behind counselling
- The type of counselling setting suitable to the patient
- The stage of the patient's care pathway

The Objective. As per the 'Patient's Charter for Tuberculosis Care', patients have the right to Care, Dignity, Information, Choice and Confidence.[18] The objective of counselling is to meet the needs and ensure the rights of the patient. The objective is also to support the patient where possible to overcome barriers to successful treatment.

The Type. Counselling can take place through providers adequately trained to identify the needs of the patient, through community engagements, support groups, and individual counselling.[16]

The Stage. *Before diagnosis* is confirmed, the patient must be informed of and understand all relevant information about the disease, its symptoms, the tests, the need for follow-up and treatment, and that it is treatable and curable.

Once diagnosis is confirmed and treatment is to be initiated, the patient must understand the regimen and its duration, the details of adverse drug reactions and what action to take if they encounter them, the importance of adherence and nutrition, the importance of infection

control. It is equally important to enlist family support (if consented to) for the patient to successfully complete treatment. Once TB is diagnosed, it is important for the patient to also undergo HIV testing, and testing for other comorbid conditions such as diabetes. These tests also require counselling and education.

After treatment is underway, along with monitoring physical and biological parameters, in order to ensure adherence, motivation and psychological well-being, it is important that the physician understands the health needs of the patients including if necessary the need to be referred to trained counsellors, community level support groups or mental health services if needed.[15]

It is important therefore to acknowledge the need for a patient centred approach to TB care and understand its benefits.

TAKING THE PATIENT CENTRED APPROACH

The 'Patients Charter for TB Care', states that each patient has a "right to receive timely, concise, and clear description of the medical condition, with diagnosis, prognosis (an opinion as to the likely future course of the illness), and treatment proposed, with communication of common risks and appropriate alternatives."[18] It is this information, which is often overwhelming for the patient, where counsellors can ensure the patient has a foundation in understanding the illness and the critical importance of treatment adherence. Patient programmes integrating counselling services can also significantly improve treatment adherence and the use of a multimodal approach is more effective in improving adherence than stand-alone programmes.[19]

An integral measure therefore in ensuring these patients receive the care they need and continue with their treatment regimen is providing counselling services to strengthen the support system throughout their treatment timeframe. The model of implementing counselling as a supplement to treatment is not a novel technique, and has been successfully implemented for diseases such as HIV/AIDS.

Recognizing the importance of providing patient support services that include counselling, the RNTCP has also undertaken a project for providing integrated counselling services to TB patients. In May of 2014, in partnership with Population Services International, Project Axshaya was implemented to provide facility and home based counselling for DR-TB patients across 28 districts with the help of 30 DR-TB trained counsellors. Project Axshaya is implementing strategies that will increase capacity for healthcare providers and ensure patients are equipped with the knowledge to maintain treatment.[20]

Another example of a point-of-care and community-based counselling is the Saksham project. Saksham, is implemented by the Tata Institute for Social Sciences (TISS) and was developed to strengthen human and institutional capacities of the national health system in the field of HIV/AIDS counselling. Mumbai which is implementing counselling services for. Counselling services for HIV/AIDS patients have ensured patients understand the disease as well as limit risky behaviours which can increase the spread of the disease. Owing to the success of Project Saksham, TISS is leading the way in integrating counselling services for TB patients and families, building capacity through training healthcare providers and ensuring patients receive supportive supervised care while being treated for TB.[21]

It is evident that scaling successful models such as the ones implemented by Project Saksham and Project Axshaya are essential in ensuring TB patients are able and empowered to adhere to treatment guidelines. Implementing this approach will enable the patient to access the best possible care. Creating an environment which is supportive of TB patients is integral in addressing the societal problems faced by patients, and will strengthen the patients resolve while going through the treatment process.

TB patients continue to experience difficulties in navigating the path from diagnosis to cure and find it personally distressing. With the help of a dedicated counsellor, the journey to a TB free life would be much easier and is something which is not too difficult to provide. Rather than focusing on just the disease, it is imperative to treat the patient as a whole. We must use patient centred approaches, and recognize that all TB patients deserve a minimum package of holistic TB care services that are not restricted to diagnosis and pharma-

Notes from a MDR-TB Patient Advocate

- Patients constantly need someone to motivate them and help them sail through this phase of life
- A counsellor can guide the patients and advise them on how to deal with their day-to-day problems
- Patients need a good listener who will hear them out and guide them appropriately
- A patient needs hope, hope that she/he will come out of all this and hope that there will be a better future. Who better than a counsellor can give her/him that?

Watch "Deepti's Story : From Survivor to a Champion" on YouTube - https://youtu.be/hvaormVq0vE

Key take away messages for healthcare providers

ALL TB PATIENTS DESERVE A MINIMUM PACKAGE OF COUNSELLING AND TB SERVICES

- **Use good communication principles when counselling all patients**
- **Explain the details of TB:**
  - –What TB is?
  - –How the disease spreads?
  - –Signs and symptoms
  - –Consequences of not following treatment guidelines
  - –Why treatment is long and why completion of treatment is critical?
  - –Likely adverse events during therapy
  - –Cost involved in treatment and what free/public services are available to patients
- **Identify TB diagnosis and treatment services available to the patient at all government health facilities free of cost**
- **Explain that TB is a fully curable and treatable disease**
- **Listen to the patient and assure them the services they need are available**
- **Refer to mental health services for further psycho-social support where required**

cological treatment, but include counselling and support services as well.

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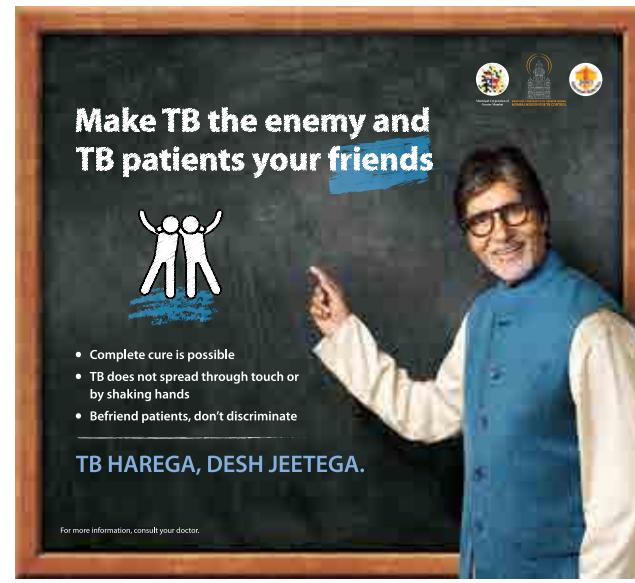

Call to Action for A TB-Free India

Kavita Ayyagari, MA and Jamhoih Tonsing, MBBS, DPM, MSc—Authors*

There were more than 20 deaths in a month due to Dengue in Delhi[1] in 2015. There was a big hue and cry, and newspapers carried stories daily on the Dengue toll. There was the heart-breaking story of the little boy who died of Dengue because no hospital would take him. His parents committed suicide after his death.[2] The State and the administration and the hospitals were all made accountable. One story shook the nation for the entire week. Dengue is a notifiable disease and it seems the state departments do get notifications for it[3] and the state departments get rapped if there is inadequate attention on prevention and care as the public and media pressure is tremendous.

There are at least 21 deaths for TB in a day[4] in the city of Mumbai alone. Across the country, 2 people die every 3 minutes[5] due to TB, according to government figures. Somehow these stories never make any headlines. No one really knows what happened as someone quietly passes away from TB. No hue, no cry. No heart-breaking story here. One wonders why?

The TB situation in India is fairly alarming. India accounts for 23% of the TB burden in the world. Being the second most populous country, the numbers are, of course, large. But for an ancient airborne infectious disease that has survived centuries, the numbers can be ominous as with every one case that goes undetected or untreated, new cases will appear. A person who has active pulmonary TB can infect 10-15 others in the year, and remain infectious for 2 to 3 years if left untreated.[6]

India recorded the largest number of TB cases in the world last year.[7] 1.5 million people died in 2014 from the disease which now ranks alongside HIV as a leading killer worldwide.[8] 140,000 amongst them were children.[9] Most of these deaths could have been prevented.

If unchecked, TB can become India's most serious health crisis, acting as an obstacle to India's progress in the years to come. It is imperative that India takes strong, coordinated action and addresses issues of TB prevention, diagnosis, access to treatment and support in the coming years.

The Government alone cannot tackle the TB monster. There is need for all round support from all stakeholders and partners, to ensure early and accurate diagnosis, correct treatment, treatment adherence, and economic support to families.

As reviewed in the earlier chapters of this book, the symptoms of TB are persistent cough and fever, loss of weight and appetite. People generally turn to the private doctor when they experience these symptoms. The first point of contact is the family physician or the doctor next door. It largely rests on the private sector to be able to diagnose TB early and advise treatment. This, in turn, requires them to test for TB, using WHO or RNTCP-approved diagnostics. If TB is confirmed, then it is critical for doctors to start the correct drug regimen and help patients complete the full course of therapy.

*The views expressed here are the authors' personal views and do not necessarily represent the views of the US Government or USAID.

Call to Action for a TB-Free India

The Call to Action for a TB-Free India echoes WHO's 'End TB Strategy' and calls for the country to intensify TB care and prevention efforts to end TB in India. The vision of the End TB Strategy is ***A World free of TB: Zero TB deaths, Zero TB disease, and Zero TB suffering***.

Shri J.P. Nadda, Hon'ble Minister of Health & Family Welfare, Government of India, launched the **Call to Action for a TB-Free India on April 23, 2015**.

The objectives of the Call are:

- Mobilize a wide range of stakeholders to demand and sustain high-level domestic commitment to end TB in India; and
- Tap the energy and influence of key stakeholders to drive political, administrative, and technical solutions to address specific barriers affecting TB care and prevention in India.

Under the stewardship of the Ministry of Health and Family Welfare, The International Union against TB and Lung Diseases (The Union) is implementing the Call to Action seeking to engage a wide range of stakeholders and mobilize domestic resources and commitment to end TB in India. The project is funded by the United States Agency for International Development (USAID) through the **Challenge TB project**.

For more information:
write to tbfreeindia@theunion.org or contact
The Challenge TB Team, The Union South-East Asia Office
C-6, Qutub Institutional Area,
New Delhi 110 016, India.
Tweet at @forTBfreeindia

With TB, a person needs medical leave that may go beyond the usual sick leave. S/he requires leave for the period they are infectious. Therefore, TB patients need a workplace where their condition is recognized and they are not discriminated for. Thus, businesses, organizations and employers have a key role to play in the fight against TB.

Stigma is still an issue with TB in India, and patients may feel alienated or isolated within their communities or families. People may fear the disease and want nothing to do with persons suffering from TB. Young girls with TB may never get married because of stigma. Mothers may not be given care in the family and be forsaken or even sent back home, if they had TB. Families are broken when the main breadwinner cannot earn a living because of TB.

The good news is that TB is a treatable and curable disease. Therefore awareness is critical. The Call to Action for a TB-Free India is a call to make India free from this disease and all of us must join to make a difference.

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Adverse Drug Events With Anti Tuberculosis Therapy:

What Every GP Should Know

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Abstract

The success of tuberculosis treatment rests on multidrug antituberculosis therapy at least for six months. During the prolonged course of therapy, patients and providers may confront many adverse drug events (ADE). While minor ADE are common, some are rare and potentially life threatening. Hence it becomes obligatory for the providers to anticipate ADE during therapy, and take necessary measures when ADE occur. The common adverse events are mild elevation of liver enzymes, skin rash, gastrointestinal intolerance, neuropathy and arthralgia and can be managed symptomatically without discontinuation of the offending drugs. Serious adverse events are severe hepatitis, Steven Johnson syndrome, immune thrombocytopenia, agranulocytosis, hemolysis, renal failure, optic neuritis and ototoxicity. These warrant immediate stoppage of drugs and in some cases contraindicate re-challenge. Single most important factor to prevent adverse patient outcomes in terms of severe/chronic disease or fatality is prompt recognition of ADE, discontinuation of the probable drug/s with appropriate evaluation and management. Patients must be educated about symptoms of adverse events and asked to report them promptly. Prevention of monotherapy during the management of ADE is critical to prevent emergence of drug resistant TB.

Key words: *tuberculosis; treatment; adverse drug events; drug reactions; monitoring.*

According to the Standards of TB Care in India,1 pulmonary tuberculosis patients are to be treated with Isoniazid (INH), Rifampicin (RIF), Pyrazinamide (PZA) and Ethambutol (EMB) as the first line therapy given as intensive phase for first two months followed by INH, RIF and EMB in the continuation phase for next four months. The course of treatment can be complicated by occurrence of adverse events necessitating treatment interruptions and modified regimens. Lack of adherence to drugs and treatment interruptions are the driving factors for emergence of drug resistance during the treatment.

Adverse drug events (ADE) during anti-tuberculosis therapy (ATT) contribute to 7% of all drug related adverse events and 30% of fulminant hepatitis. This review is limited to the common adverse drug events on first line ATT which are extensively used by general practitioners. Patients requiring second line drugs are best managed by pulmonary or infectious diseases physicians.

So, adverse events during second-line therapy are not discussed in this review. The most common ADE while on ATT, namely drug induced hepatitis, skin rash, gastro-

intestinal and neurological events, will be discussed in detail. Table 1 provides an overview of the common ADEs during ATT.

Table 1 — Common adverse events with first line ATT drugs

Drug	Common adverse events
Isoniazid (INH)	Asymptomatic transient elevation of transaminases (20%), hepatitis, peripheral neuropathy, fever, skin rash, seizures, psychosis
Rifampicin (RIF)	Reddish orange color of urine and tears, Pruritus, GI intolerance, Isolated hyperbilirubinemia, hepatitis, pancytopenia, flu like syndrome, acute kidney injury
Pyrazinamide (PZA)	Nausea, vomiting, hepatitis, arthralgia, hyperuricemia, skin rash
Ethambutol (EMB)	Optic neuritis (1-5%), peripheral neuropathy, skin rash
Streptomycin (SM)	Ototoxicity, nephrotoxicity, skin rash

DRUG INDUCED LIVER INJURY

Drug induced liver injury is the most severe of the ADE. Occurrence of ATT induced hepatitis is estimated to be 5-33%, depending on the definitions used to diagnose hepatitis.2 Most widely used definition of drug induced hepatitis is serum aminotransferase level >5 times the upper limit of normal [ULN] without symptoms or >3 times the ULN with symptoms of hepatotoxicity like nausea, vomiting, or pain abdomen.2,3 ATT may be associated with asymptomatic elevation of transaminases in about 20% of patients. It may also result in acute hepatitis, even subacute to fulminant hepatitis, which may be fatal.

The frequency of hepatitis associated with rifampicin is 0.6-2.7%, while that with Isoniazid is 0.6%.4 Among the first line ATT drugs, PZA is the most hepatotoxic, with 15% of patients experiencing hepatic adverse events when higher dose of PZA is used.5 The risk of hepatitis is more with combination of INH with RIF or PZA.

TYPES OF HEPAT OTOXICITY AND CLINICAL FEAT URES

- Hepatic adaptation. Transient asymptomatic elevation of alanine aminotransferase (ALT) may be seen as a physiological response to drug exposure because of Cytochrome P450 enzyme induction.
- Drug induced acute hepatitis. It is associated with hepatocyte necrosis and elevation of hepatic transaminases with or without jaundice. Patients may be asymptomatic or may present with nausea, vomiting, abdominal pain and jaundice. Occasionally they may report constitutional symptoms including fever. INH and Rifampicin can produce hepatotoxicity by this mechanism.
- Granulomatous hepatitis. e.g. Pyrazinamide can produce this and it is a hypersensitivity reaction to the inciting drug with granuloma formation. Patients may present with fever, lethargy, body ache, rash, lymphadenopathy and hepatosplenomegaly. Biochemical examination will reveal elevation of serum transaminases along with alkaline phosphatase.
- Cholestasis. Usually associated with asymptomatic elevation of alkaline phosphatase along with bilirubin because of failure of bilirubin transport. e.g. seen with rifampicin.

RISK FACTORS FOR HEPAT OTOXICITY:

- Age >35 years
- Children
- Female gender
- Recent child birth (<3 months post-partum)
- Alcohol abuse
- Abnormal baseline liver enzymes
- Slow acetylator status- associated with INH associated hepatotoxicity
- Malnutrition/hypoalbuminemia

RECOGNITION OF DRUG INDUCED HEPAT ITIS

It is important for doctors to suspect drug induced liver injury when patients on ATT present with nausea, vomiting, right hypochondriac pain, and jaundice. Temporal pattern of disease evolution after exposure to drugs is important to diagnose drug induced adverse events. Liver function tests must be requested on suspecting liver injury. Drug induced hepatitis is diagnosed when serum aminotransferase level >5 times the ULN without symptoms or >3 times the ULN with symptoms. Bilirubin may or may not be elevated. Early detection of drug induced liver disease is critical to prevent severe or chronic liver disease. Patients should be advised to report any untoward symptoms, like nausea, malaise, lethargy, right hypochondriac pain or new onset fever.

MANAGEMENT OF PAT IENTS WITH DRUG INDUCED HEPAT OTOXICITY

Once hepatotoxicity is suspected, all hepatotoxic drugs must be stopped and promptly

CLINICAL HIGHLIGHTS

❑ The course of treatment of TB can be complicated by drug induced adverse events and GP's knowledge about their occurrences and competency to diagnose them are critical for the successful outcome.

❑ Minor adverse reactions to TB medications include nausea, gastric intolerance, neuropathy, itching and joint pains that can be managed symptomatically and do not warrant stoppage of medications.

❑ Major adverse reactions include hepatitis, severe skin reactions, optic neuropathy thrombocytopenia, hemolysis, and renal failure. Symptoms and signs suggesting a major reaction should be treated by stoppage of drugs, and close monitoring.

❑ Drug induced liver injury is the most common serious adverse event which may present as nausea, vomiting, jaundice, right hypochondriac pain and requires stoppage of all hepatotoxic drugs with monitoring of liver functions and subsequent reintroduction of drugs sequentially.

❑ Patients with pre-existing liver disease, viral hepatitis, chronic alcohol consumption, pregnant women, or postpartum period, HIV infection and on concomitant hepatotoxic medications are particularly at high risk of ATT induced hepatitis and these risk factors must be carefully sought prior to the initiation of ATT and are to be monitored with LFT every 2-4 weekly on therapy.

❑ On reintroduction of ATT, it is important to avoid mono therapy to prevent emergence of drug resistant TB. Non hepatotoxic drugs like streptomycin, ethambutol and moxifloxacin can be given, when hepatotoxic drugs need to be stopped.

❑ Life threatening complications like immune thrombocytopenia, immune hemolytic anemia, Steven Johnson syndrome, and organ threatening complications such as ototoxicity, nephrotoxicity, and ocular toxicity are absolute contraindications to rechallenge with the suspected drug.

❑ All patients need to be counselled on how to identify ADEs, before initiation of ATT.

investigated as mentioned above. Failure to discontinue a drug that is causing liver injury leads to poor outcome such as acute liver failure or chronic hepatitis. The specific risk factors for drug induced hepatotoxicity have to be carefully elicited. In all patients with liver abnormality, history of hazardous intake of alcohol, other hepatotoxic drug ingestion must be enquired about and viral hepatitis must be ruled out. No hepatoprotective agent has been effective in ameliorating drug induced liver damage. Non hepatotoxic ATT drugs which could be used are streptomycin, ethambutol and levofloxacin or moxifloxacin.

Patient should be observed for progress and the liver function tests [LFT] should be monitored once in 3 days. Usually symptoms and laboratory abnormalities promptly improve within days or weeks once the inciting drugs are stopped. When the ALT returns to less than 2 times the ULN, gradually drugs are reintroduced sequentially with rifampicin, INH and PZA in that order with a gap of 3-7 days between each drug and monitoring of LFT.2 If symptoms recur or ALT increases, the last drug added should be stopped. In those patients who had experienced severe or prolonged hepatotoxicity, reintroduction of PZA may be avoided and the duration of ATT may be extended to 9 months.

GA STROINTESTINAL ADVERSE EVENTS

GI adverse events are usually minor. They include nausea, vomiting and abdominal discomfort, which may be selflimiting. This may be due to mild gastritis and can be managed by the addition of proton pump inhibitors, anti-emetics, administering drugs after meals or by giving drugs at an interval. Discontinuation of ATT is usually not required. However, in all such patients with the above mentioned symptoms, LFT must be requested to rule out early liver toxicity.

DERMAT OLOGICAL ADVERSE EVENTS

Skin related ADE can occur with all anti TB drugs and is one of the commonest side effects in up to 6% of patients on ATT.6 It can be in varying forms like maculopapular rash, erythema multiforme syndrome, acneiform eruptions, urticarial, lichenoid eruptions, and the more severe exfoliative dermatitis and Steven Johnson Syndrome. Exfoliative dermatitis also called erythroderma, a form of cutaneous hypersensitivity occurs after 6-8 weeks of therapy. The propensity of the drugs to cause erythroderma is PZA >SM >EMB >RIF >INH with rates for PZA being 2.4%.6 Steven Johnson syndrome is a life threatening muco- cutaneous syndrome and it has been described with RIF, INH, PZA and thiacetazone.[7]

In patients with itching/ minimal rash, ATT can be

continued along with symptomatic treatment with antihistamines have to be prescribed. Reintroduction of the ATT is to be done with INH followed by RIF, EMB and PZA with careful monitoring.

NEUROLOGICAL ADVERSE EVENTS

CNS adverse events include seizures, psychosis, ototoxicity, and optic neuritis.8 The drug most commonly implicated in psychosis is INH followed by cycloserine. Seizures are a side effect of INH, fluoroquinolones, and cycloserine. Ototoxicity and neuromuscular blockade are adverse events of aminoglycosides, while ethambutol is known to cause optic neuritis. Ototoxicity and optic neuritis are dose dependent.

It is important to ask patients about tinnitus, imbalance, vertigo or decreased hearing while the patients are on aminoglycosides. As children may not be able to complain about decreased vision, or impairment of color perception (which is a classical symptoms of optic neuritis), ethambutol is best avoided in children Peripheral neuropathy, manifested by tingling and numbness in hands and feet is a side effect of INH (seen in up to 2% of patients), less commonly ethambutol and ethionamide.

The risk factors for peripheral neuropathy are malnutrition, HIV infectioninfection, diabetes mellitus, alcohol abuse and concomitant drugs having neuropathy potential such as Stavudine. It is best to prevent peripheral neuropathy by pyridoxine supplementation (40mg daily) to all patients with the neuropathy risk factors receiving INH. The involved drugs have to be stopped promptly on the first suspicion of seizures, psychosis, ototoxicity or visual toxicity and never administered again.

MUSCULOSKELETAL ADVERSE EVENTS

Mild arthralgia may be associated with PZA, and is associated with elevated uric acid. It can be managed symptomatically with NSAIDS.

RENAL ADVERSE EVENTS

Acute kidney injury (acute renal failure) with normal urine output can occur with aminoglycosides. Rarely, rifampicin can give rise to interstitial nephritis.

DRUG INDUCED HAEMAT OLOGICAL ADVERSE EVENTS

Immune mediated cytopenia of all three cell lines, including agranulocytosis have been described with ATT. Thrombocytopenia is an uncommon but potentially life-threatening complication and is characterized by rapid destruction of platelets in susceptible patients due to immune mechanisms. Patients usually present with purpuric rashes all over the body. Although this has been reported classically with RIF; PZA, EMB and INH are also implicated in various case reports.9 The diagnosis is by resolution of symptoms and improvement of platelet count on stopping the drugs. Treatment is by discontinuation of the drugs, transfusion of platelets if platelet count is <20,000/µL. Patient has to be managed with 3 new anti tuberculosis drugs including one parenteral agent.

Rifampicin is also implicated with life threatening drug induced hemolytic anemia due to immune mechanisms.10 It can manifest with severe anemia requiring blood transfusion and jaundice due to indirect hyperbilirubinemia. Re-challenge with the offending drug is contraindicated both in drug induced thrombocytopenia and hemolysis as minute quantity of the drug can trigger a very severe reaction.

MONITORING OF PAT IENTS FOR ADE ON ATT

All patients should undergo baseline testing of serum bilirubin, transaminases, alkaline phosphatase, creatinine, and complete blood count. In those with risk factors for hepatotoxicity, every 2-4 weekly monitoring of liver function tests is recommended. In those without risk factors, routine LFT monitoring is not required unless symptomatic. During each visit, patients should be asked about symptoms of possible ADE relevant to the regimen they are receiving. ■

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CIS CME–Questions

Adverse Drug Events With Anti Tuberculosis Therapy:
What Every GP Should Know

Questions

1 Which of the following drugs has the highest potential to produce exfoliative dermatitis?

a. Isoniazid
b) Rifampicin
c) Pyrazinamide
d) Ethambutol

2 Which of the following adverse events is a contraindication to rechallenge of the possibly implicated drug during treatment with ATT?

a. Hepatotoxicity
b. Drug rash
c. Drug induced thrombocytopenia
d. Vomiting

3 Which of the following ATT drugs has no hepatotoxicity potential?

a. Rifampicin
b. Pyrazinamide
c. Isoniazid
d. Ethambutol

4 Which of the following is a risk factor for ATT induced hepatitis?

a. Female gender
b. Advancing age
c. Malnutrition
d. All of the above

5 Which of the following is false regarding adverse reactions to TB drugs?

a. Jaundice is a common adverse effect and is always due to liver adaptation which is self-limiting.
b) Drug induced neuropathy can be prevented by routine supplementation with pyridoxine
c) Joint pains are an adverse reaction to pyrazinamide and usually respond well to non-steroidal anti-inflammatory drugs
d) Females and those with pre-existing liver disease are more susceptible to drug induced hepatitis

(See answers on the next page)

CIS CME–Answers

Adverse Drug Events With Anti Tuberculosis Therapy:
What Every GP Should Know
Questions on the previous page

Answers

1 **The correct answer is (c).** The propensity of the drugs to cause erythroderma (exfoliative dermatitis) are PZA >SM >EMB >RIF >INH with rates for PZA being 2.4 %. All the drugs have to be stopped and reintroduction of the ATT is to be done with INH followed by RIF, EMB and PZA with careful monitoring. To prevent monotherapy, 2 new drugs which were not used previously should be added while introducing individual drugs.

2 **The correct answer is (c).** Drug induced thrombocytopenia is because of immune mediated mechanisms because of production of autoantibodies or drug dependent antibodies resulting in rapid destruction of platelets. It is a life threatening complication and is an absolute contraindication to rechallenge as even minute quantities of the drug can trigger immune mediated destruction of platelets leading to severe hemorrhage.

3 **The correct answer is (d).** The propensity to produce hepatotoxicity is with PZA> INH> RIF. Ethambutol, streptomycin and moxifloxacin do not have hepatotoxic potential and they can be administered safely in patients with hepatotoxicity while discontinuing those drugs with hepatotoxic potential and to accompany the individual drugs on rechallenge to prevent monotherapy .

4 **The correct answer is (d).** Advancing age, female gender, chronic alcohol consumption, pre existing liver diseases, hepatitis B, C and HIV coinfection, malnutrition are some of the important risk factors for drug induced hepatotoxicity. They have to be carefully sought prior to the initiation of ATT and their presence warrant close monitoring of liver function tests every 2-4 weeks on therapy.

5 **The correct answer is (a).** Jaundice is a sign of hepatitis and warrants stoppage of all TB medications, and investigations for druginduced hepatitis. However, it can also occur rarely due to drug induced hemolysis which is a life threatening complication. Liver function tests and complete blood counts are to be requested to differentiate drug induced hepatitis and hemolytic jaundice. Drug induced hepatitis is diagnosed when serum aminotransferase level >5 times the upper limit of normal [ULN] without symptoms or >3 times the ULN with symptoms

Drug-Resistant Tuberculosis:
10 Principles for Effective Management

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Multidrug-resistant (MDRTB) and extensively drug-resistant TB (XDR-TB) are demanding conditions to treat and are best managed by a specialist with experience in treating such severe forms of TB. Alternatively, such patients are best referred to the national TB program (RNTCP) where they are now offered the standardised Category 4 or Category 5 treatment depending on whether they are MDR or XDR, respectively. So, GPs should always seek help in the management of MDR and XDR-TB.

MDR-TB refers to *M. tuberculosis* resistance to at least isoniazid and rifampicin, the two key first-line antibiotics. Extensively drug-resistant (XDR) TB disease, which causes even more-severe disease manifestations, is not only resistant to isoniazid and rifampicin, but also any fluoroquinolone and any of the three injectable second-line antibiotics.

Even in the best hospitals, under optimal conditions, global treatment success rates are in the vicinity of 60% for MDR-TB and 44% for XDR-TB. Errors in treatment amplify resistance and convert MDR strains to XDR-TB and beyond. The 10 principles outlined here maximise the chances of successful outcome.

PRINCIPLE 1: Plan your regimen based on a careful drug history coupled with the drug susceptibility test (DST) report from a reliable, quality assured, laboratory. DST requires liquid cultures, supplemented with rapid molecifular tests such as Xpert MTB/RIF, and line probe assays (Hain Genotype MTBDRplus for first-line drugs, and Hain Genotype MTBDRsl for second-line drugs).

PRINCIPLE 2: Include the right number of drugs (**Table** shows the available drugs, categorized into groups by WHO). Too many drugs risks toxicity, while too few increases the risk of treatment failure. WHO recommends 4 new drugs (to which the TB bacteria are sensitive) while a more recent article suggests 6 drugs may be ideal.

PRINCIPLE 3: Select drugs from the following groups when composing the regimen:

i. include any first-line drugs to which the patient is still sensitive e.g., ethambutol or pyrazinamide. These should be included but not "counted" as one of the 4 new drugs.

ii. use a Group A fluoroquinolone (FQ). Levofloxacin and moxifloxacin are the preferred FQ's. The exact doses are unclear but most experts feel up to 1000mg of levofloxacin and 600mg of moxifloxacin per day might be ideal.

iii. use a Group B 2nd line injectable aminoglycoside to which the organism is sensitive. The injectable should be used for at least 6-8 months, ideally 5 days a week.

iv. add Group C drugs to make up the desired 5 drugs in the regimen. These drugs (e.g., cycloserine, ethionamide) are bacteriostatic and have considerable toxicity. The WHO recommends that ethionamide, being the most effective, should be introduced first.

v. add other Group C or D3 drugs if the requisite number of drugs has not been met yet, depending on disease burden and pattern of resistance. The most effective but most toxic drug in this group is linezolid. This drug should, however, be used with great caution because of the high risk of toxicity. Toxicities frequently encountered include peripheral neuropathy, anemia and optic neuritis. Clofazamine is an old but useful drug and should be added to most regimens. Meropenem-clavulanate is extremely expensive and since it is administered intravenously, ideally needs a IV port to be inserted, which adds to the cost. The new 2016 WHO guidelines differ from the earlier guidelines in that they have specifically dropped clarithromycin (which is useful for *Mycobacterium avium complex* (MAC) infections but not for *M. tuberculosis*), and amoxicillin/clavulanate (which has no anti-mycobacterial activity on its own).

vi. try and access new drugs (D2) for highly resistant strains. Bedaqualine (Sirturo®) and Delamanid (Deltyba®) are both difficult to access in India, but should be considered for 6 months for highly resistant strains or treatment failures

Table. WHO classification of TB drugs used for MDR-TB[1]

A. Fluoroquinolones[2]		Levofloxacin	Lfx
		Moxifloxacin	Mfx
		Gatifloxacin	Gfx
B. Second-line inhectable agents		Amikacin	Am
		Capreomycin	Cm
		Kanamycin	Km
		(Streptomycin)[3]	(S)
C. Other core second-line agents[2]		Ethionamide / Prothionamide	Eto / Pto
		Cycloserine / Terizdone	Cs / Trd
		Linezolid	Lzd
		Clofazimine	Cfz
D. Add-on agents (not part of the core MDR-TB regimen)	**D1**	Pyrazinamide	Z
		Ethambutol	E
		High-dose isoniazid	Hh
	D2	Bedaquilline	Bdq
		Delamanid	Dlm
	D3	Para-aminosalicylic acid	PAS
		Imipenem-cilastatin[4]	Ipm
		Meropenem[4]	Mpm
		Amoxicillin-clavulante[4]	Amz-Civ
		(Thioacetazone)[5]	(T)

1. This regrouping is intended to guide the design of conventional regimens; for shorter regimens lasting 9-12 months the composition is usually standardised (See WHO MDR-TB guidelines)
2. Medicines in Groups A and C are shown by decreasing order of usual preference for use
3. Refer to the WHO guidelines for the conditions under which streptomycin may substitute other injectable agents. Resistance to streptomycin alone does not qualify for the definition of extensively drug-resistant TB (XDR-TB)
4. Carbapenems and clavulanate are meant to be used together; clavulanate is only available in formulations combined with amoxicillin
5. HIV-status must be tested and confirmed to be negative before thioacetazone is started

Source: WHO, Geneva http://www.who.int/tb/MDRTBguidelines2016.pdf

PRINCIPLE 4: Treat for the right duration. The current WHO recommendation for total duration of treatment stands at around 22 months. The Bangladesh regimen, which WHO calls the Shorter MDR-TB regimen, is an exciting new development, which attempts to shorten the duration of treatment to just 9-12 months. According to the updated 2016 WHO guideline, in selected patients with rifampicin-resistant or MDR-TB who have not been previously treated with second-line drugs and in whom resistance to fluoroquinolones and second-line injectable agents has been excluded or is considered highly unlikely, this shorter regimen of 9-12 months may be used instead of a conventional regimen. Sadly, a majority of Indian MDR-TB patients are likely to have been already treated before seeing a specialist, and hence it is unlikely this regimen would work in a high burden country like India.

PRINCIPLE 5: Use the right doses at the highest end of the range to compensate for the inherent weakness of these drugs. Bear in mind that wrong doses contribute to treatment failure and toxicity. Therapeutic drug monitoring (TDM) is useful but is available in no more than a handful of centres across the world.

PRINCIPLE 6: Treatment should be administered daily (no role for intermittent therapy here) and ideally under close supervision (e.g., directly observed therapy). Regular cultures are necessary to monitor treatment efficacy.

PRINCIPLE 7: Monitor closely for toxicity. Major adverse effects (including life threatening ones) occur in as many as 40-60% of MDR and XDR cohorts and must be anticipated and carefully monitored for.

PRINCIPLE 8: Early surgery should be considered whenever feasible. Indeed, the more resistant strain, the lower the threshold for surgery. Surgery must be performed by an experienced surgeon in the patient with localised disease, with enough respiratory reserve to withstand this often high-risk procedure.

PRINCIPLE 9: Empathise, support and motivate. This prolonged and toxic treatment will only succeed with patient-centric support from the treating physician.

PRINCIPLE 10: Address the social determinants and comorbid conditions that often accompany TB. TB is a social disease and a holistic approach that attempts to improve the general poverty, malnutrition, smoking, biomass exposure, and diabetes that often co-exist is of vital importance. ■

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Multidrug-Resistant Tuberculosis (MDR TB)—Fact Sheet

1 How does drug resistance happen?

Resistance to anti-TB drugs can occur when these drugs are misused or mismanaged. Examples include when patients do not complete their full course of treatment; when health-care providers prescribe the wrong treatment, the wrong dose, or length of time for taking the drugs; when the supply of drugs is not always available; or when the drugs are of poor quality.

2 Who is at risk for getting MDR TB?

Drug resistance is more common in people who:

- Do not take their TB medicine regularly
- Do not take all of their TB medicine as told by their doctor or nurse
- Develop TB disease again, after having taken TB medicine in the past
- Come from areas of the world where drug-resistant TB is common
- Have spent time with someone known to have drug-resistant TB disease

3 How can MDR TB be prevented?

The most important thing a person can do to prevent the spread of MDR TB is to take all of their medications exactly as prescribed by their health care provider. No doses should be missed and treatment should not be stopped early. Patients should tell their health care provider if they are having trouble taking the medications. If patients plan to travel, they should talk to their health care providers and make sure they have enough medicine to last while away.

Health care providers can help prevent MDR TB by quickly diagnosing cases, following recommended treatment guidelines, monitoring patients' response to treatment, and making sure therapy is completed.

Another way to prevent getting MDR TB is to avoid exposure to known MDR TB patients in closed or crowded places such as hospitals, prisons, or homeless shelters. If you work in hospitals or health-care settings where TB patients are likely to be seen, you should consult infection control or occupational health experts. If the patient with DR-TB wears a mask he/she can reduce the transmission of TB to household contacts.

Source: CDC, USA http://www.cdc.gov/tb/publications/factsheets/drtb/mdrtb.htm

Monitoring and Improving Adherence to Tuberculosis Medications

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Abstract

Today, about 10% to 50% of all TB patients in India fail to complete treatment, depending on the type of TB the patient has. The consequences of poor adherence to TB treatment are disastrous, increasing the risk of patient morbidity and mortality, disease relapse, drug-resistance, and transmission of TB. While the Revised National TB Control Programme (RNTCP) has long relied upon direct observation of therapy (DOT) for TB patients, this monitoring strategy requires greater resources than are available to most GPs. New technologies for monitoring medication adherence—including cellphone-based strategies and electronic pillboxes—may soon become available to GPs in parts of India and provide alternative strategies for monitoring pill-taking by patients in real time. Once a GP identifies medication non-adherence, she or he should screen for and address toxicities from TB medications, poor nutrition and other comorbidities (e.g., HIV, diabetes), psychosocial barriers (e.g., depression, stigma, substance use disorders) and poor treatment literacy that could be contributing to non-adherence. Improving TB medication adherence therefore requires an interdisciplinary approach.

INTRODUCTION

You have just informed your patient that she is to start TB treatment immediately. She has to take 4 drugs for 2 months, and continue to take 2 or 3 drugs for another 4 months. You know that this is a long and tedious regimen. You know that she will probably develop some side effects. You hope that she will not develop drug-resistance. You know that she is probably dealing with more in her life than just TB. But you know that the only way she can be cured is if she adheres to the full course of treatment. You will see her once a month for about 10 minutes. How are you going to monitor her medication adherence and support her in achieving this outcome?

Today, about 10% to 50% of all TB patients in India fail to complete treatment, depending on the type of TB the patient has.[1] The consequences of poor adherence to TB treatment are disastrous, increasing the risk of patient morbidity and mortality, disease relapse, drug-resistance, and transmission of TB.[2,3] In this chapter, we discuss strategies for GPs to monitor and improve a TB patient's medication adherence.

MONITORING ADHERENCE TO TB MEDICATIONS

For more than a decade, India's Revised National TB Control Programme (RNTCP) has relied upon direct observation of therapy (DOT) to monitor medication adherence. DOT may be conducted at the health facility level or outsourced to family members or individuals in the community. Either way, DOT requires a trained individual to observe a TB patient take every dose of medication, which demands greater resources and supervision than are available to most GPs.

Table 1 — Examples of questions to ask tuberculosis patients at routine visits to identify non-adherence

Single screening question[8]

Have you missed any of your TB pills in the past week?

Morisky Questions[8-10] (any positive answer suggests significant non-adherence)

1. Do you ever forget to take your medications?
2. Are you careless at times about taking your medicine?
3. When you feel better, do you sometimes stop taking your medications?
4. Sometimes when you feel worse, do you stop taking your medicine?

In addition, it is unclear that DOT results in better treatment outcomes when compared to self-administered therapy (i.e., patients taking pills at home without observation).[4,5] DOT may result in loss of time, autonomy, and privacy; regular travel to a health facility may also lead to loss of money and employment.[6,7]

For most GPs, the only opportunity to evaluate TB medication non-adherence may be at brief monthly clinic visits. Single questions[8] or brief structured questionnaires, such as the Morisky scale[9] have been shown to have some value in detecting non-adherence in TB patients **(Table 1)**.[10]

In addition, new technologies for monitoring TB medication adherence are emerging in the public and private sector in India that record patients' pill-taking history via computer or cellphone applications. For example, the cellphone-based adherence monitoring strategy 99DOTS entails patients calling a phone number dispensed with each day's TB pills to report taking every dose **(Figure 1).**[11] Electronic pillboxes can record when the box containing TB drugs is opened and closed to indicate doses taken **(Figure 2).**[12] While these technologies do not guarantee pill intake, they can be useful proxies of adherence. As pill-taking records are continually updated in "real-time" and may be remotely accessed, GPs can rapidly identify non-adherent patients and contact them to intervene early, before the next clinic appointment. Electronic pill-taking histories can also be used as longer-term records to help GPs to better counsel patients during monthly clinic visits. These novel technologies are currently being tested in India. Research is needed to determine how they can be best used by GPs and to understand whether they positively impact patient care.

Figure 1 – 99DOTS, a cellphone based strategy used to monitor TB medication adherence, in which patients dial a unique phone number dispensed with each day's doses to report pill-taking. (Photo with permission from Everwell Health Solutions)

ADDRESSING TB MEDICATION NON-ADHERENCE: A FOUR-PRONGED APPROACH

The Standards for TB Care in India states, "[TB] treatment adherence goes beyond the realm of DOTS to a larger concept of treatment support system developed with mutual trust and respect between the patient, family, providers, treatment supporters and the health system at large to promptly identify and address all possible factors that could lead to treatment interruptions. This includes not only medical factors such as promptly addressing co-morbidities, substance use, adverse drug reactions and emergencies but also spans out to addressing various social, vocational, nutritional, economic, psychological stress experienced by the patient "throughout the course of treatment" (p.55).[13] In other words, in order to support patients with treatment completion, we must tackle the clinical and social determinants of non-adherence.

When a patient with poor adherence to TB medications is identified, we suggest that GPs should screen for, and address, four major issues: (1) toxicities from TB medications, (2) poor nutrition; (3) medical comorbidities, and (4) psychosocial barriers **(Figure 2).**

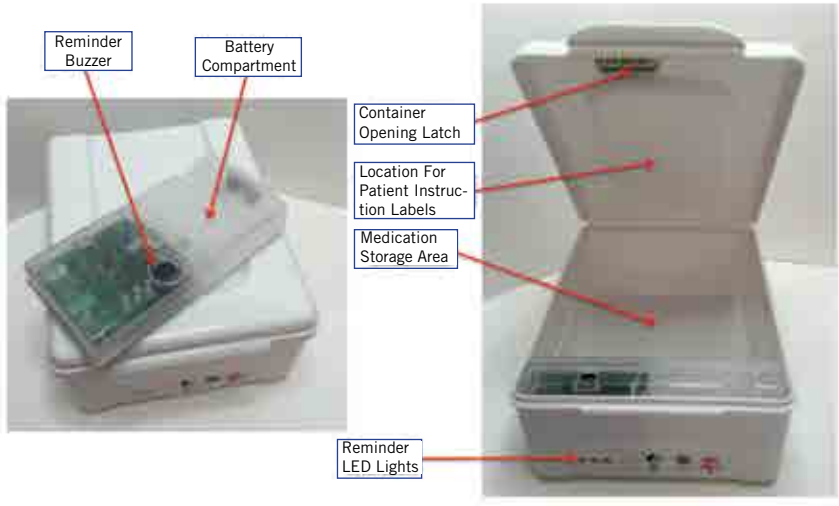

Figure 2 – The Medication Event Reminder Monitor, an electronic pillbox used to monitor TB medication adherence. The device contains an optional reminder audio buzzer and LED lights that glow everyday when the patient is scheduled to take his or her medication. Opening and closing the pillbox lid is recorded as a "dose taken" by the patient. (Photo with permission from the Arcady Group)

TOXICITIES OF TB MEDICATIONS

Medication adverse effects may be a major cause of TB treatment interruption or poor medication adherence,[14] especially for patients with multidrug-resistant TB.[15] Patients with drug-susceptible TB should be educated about common adverse effects of standard four-drug anti-tuberculosis therapy at the time of starting treatment. Early education will help ensure that harmless effects (e.g., orange-red discoloration of body fluids from rifampicin) and self-limited side effects that occur soon after starting treatment (e.g., mild gastrointestinal symptoms such as nausea without liver function abnormalities) do not result in treatment interruption. Pyridoxine (vitamin B6) supplementation at a dose of 25mg to 50mg by mouth daily should be considered for all patients with risk factors for developing peripheral neuropathy (diabetes, HIV, malnutrition, and alcohol use), since prevention of isoniazid-related peripheral neuropathy will also prevent treatment interruptions.

At follow-up visits, GPs should routinely ask about concerning symptoms associated with serious adverse effects (e.g., loss of visual acuity as a sign of optic neuritis). Early identification of potential toxicities of TB medications may help to build patients' confidence in their care providers, thereby improving adherence to medications. Detailed recommendations for screening for and managing drug toxicities are available in the chapter titled "Adverse Drug Events with Anti Tuberculosis Therapy."

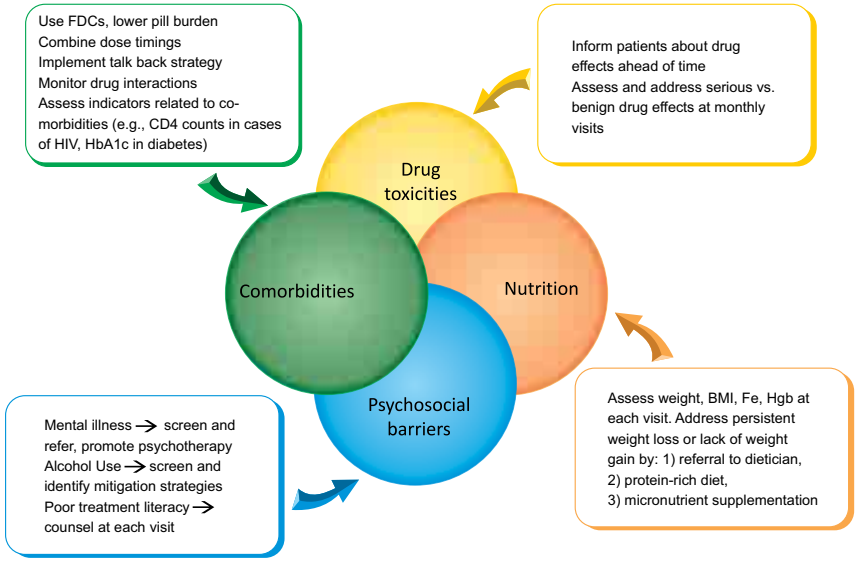

Figure 3 – Multi-pronged approach to addressing non-adherence

NUTRITION

Nutrition and TB are closely intertwined, and undernutrition may adversely impact adherence to TB medications. Poor nutrition not only compromises the immune system and puts people at risk for developing TB, it makes diagnosed TB patients more susceptible to poorer clinical outcomes, lower quality of life, and death.[16,17] Undernutrition is also a major risk factor for drug-induced hepatitis from TB medications, which could lead to treatment interruption.[18,19]

Comprehensive nutritional support of TB patients has not been shown to reduce mortality, and as such is not recommended as a standard package of care to enable adherence to TB treatment. However, nutritional supplementation may

Table 2 — Strategies to promote medication adherence in TB patients with comorbidities

1. Reduce the number of tablets by using fixed dose combinations wherever possible and eliminate unnecessary auxiliary medications
2. Simplify dose timings by combining medication doses for TB and other medical comorbidities when safe and appropriate
3. Implement a "talk-back" strategy at each visit by having the patient repeat back to you his or her understanding of the medications for each of his or her medical conditions
4. Monitor potential drug interactions and reactions, such as hypo or hyperglycemia in TB patients with diabetes (e.g., activity of sulfonylureas may be reduced with rifampicin and increased with isoniazid)

have positive impacts on patients' quality of life, including their capacity to continue to work and/or serve as caregivers. While the data are mixed, two small Indian studies suggest that provision of nutritional supplements may improve treatment completion rates[20,21] and other studies highlight improvements in physical functioning (measured using grip strength),[21,22] which could improve patients' overall participation in their TB care.

Guidance on assessing and managing nutritional status for TB patients is provided in a recent report from the Central TB Division.[23] GPs should assess patients' nutritional status at baseline and at monthly follow-up visits through clinical examination (e.g., evidence of temporal wasting), anthropometrics (e.g., height and weight to assess body mass index, mid-upper arm circumference), and labs (e.g., hemoglobin and albumin).[23] GPs should provide nutritional counseling and support in the case of any patient who fails to regain normal BMI after 2 months of treatment or who loses weight during TB treatment, with particular attention to pregnant or breastfeeding women, children under the age of 5 years, and patients with MDR-TB or HIV coinfection.[23] In these cases, GPs should consider referral to a dietician and encourage increased daily protein intake, daily micronutrient supplementation (e.g., with a multivitamin), and ensure that these patients are taking pyridoxine to prevent development of peripheral neuropathy from isoniazid.[23] Locally available nutrient-rich or fortified supplementary foods may be prescribed on a case-by-case basis. Persisting malnutrition in TB patients on treatment should raise concern for poor medication adherence or drug-resistance.

Table 3 — Screening questions to identify alcohol use disorder and depression in tuberculosis patients with poor adherence to medication

Alcohol use screening[34] (answer of >0 to second question suggests alcohol use disorder)
1. Do you sometimes drink alcoholic beverages? (If the answer is yes, ask second question)
2. How many times in the last year have you had five (four for women) or more drinks in a day?
Depression screening[35] (any positive answer suggests possible clinical depression)
1. During the last month, have you often been bothered by feeling down, depressed, or hopeless?
2. During the last month, have you often been bothered by having little interest or pleasure in doing things?

MEDICAL COMORBIDITIES

Diabetes and HIV are the most common comorbidities facing TB patients in India. TB patients who are also taking medications for diabetes or HIV may experience additional challenges in adhering to their TB treatment regimens due to a higher pill burden, drug-drug interactions, medical complications, as well as psychosocial issues. By discussing these comorbidities at each visit, and guiding patients through their multiple complex drug-regimens, GPs have the potential to improve adherence **(Table 2).** Issues specific to HIV comorbidity are discussed in the chapter "Management of HIV and TB: What Every GP Should Know."

PSYCHOSOCIAL BARRIERS TO ADHERENCE

Common psychosocial barriers that may impede patients' healthcare seeking behaviors and trigger non-adherence include poor treatment literacy,[24] alcohol use disorder,[25] stigma from TB or comorbid conditions,[26] and mental illness (especially depression and anxiety).[27,28]

Establishing basic TB treatment literacy is an important first step to promoting medication adherence.[24] Many GPs will not have counseling staff on-site or the time to deliver comprehensive patient counseling and education. Nonetheless, we recommend they cover at least 3 fundamental topics at the time of starting TB treatment: (1) explain TB disease, including potential consequences, and strategies for infection control; (2) explain the treatment regimen, including drugs, treatment duration, potential adverse effects; and (3) discuss the importance of adherence and consequences of non-adherence (i.e., mortality, transmission, relapse, drug-resistance). The chapter, "What Counselling and

Support Do Patients With Tuberculosis Need?" offers a more comprehensive framework for counseling patients with TB.

Alcohol use is common among TB patients in India and has been associated with poor treatment outcomes.[29,30] One study from South India found that 29% of TB patients currently used alcohol and 15% had alcohol use disorder (i.e., dependence or hazardous drinking behavior).[25] GPs can easily screen for alcohol disorder using brief questionnaires such as the AUDIT-C **(Table 3).** Peer-delivered psychotherapy has been shown to be helpful in alleviating alcohol use disorders in India.[31] An alcohol use intervention manual by the National Institute for Research in TB in Chennai is available online to guide GPs (http://www.nirt.res.in/pdf/AlcoholManual.pdf).[32] This intervention was recently found to increase TB treatment completion rates in a pilot study.[33] When tackling heavy drinking among TB patients, GPs can refer patients to mental health specialists and advise patients to eat before drinking, switch to low-alcohol beverages, pace the rate of drinking, and identify triggers such as peer pressure, so they may be avoided or proactively addressed.[32]

The social exclusion and stigma facing many TB patients may result in depression and contribute to poor medication adherence.[27,28,36] GPs should therefore evaluate for mental illness, especially depression, using simple screening questions **(Table 3)**. GPs should consider referring TB patients with depression to a mental health specialist. However, access to mental health specialists is difficult in many parts of India. In these settings, GPs can implement psychotherapy interventions themselves or with the help of lay counselors, as these interventions have been shown to reduce depressive symptoms in a number of communities in India.[37-39] GPs may also avail of mental health cellphone applications, developed to assist care providers in providing evidence-based mental health care related to stress and depression.[40] Psychotherapy has been shown to improve medication adherence and treatment completion in Indian TB patients.[41]

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CIS CME–Questions

Monitoring and Improving Adherence to Tuberculosis Medications

Questions

Mohan is a 53 year old man who visits your office with a month of productive cough, 8 kilograms of weight loss, and night sweats. He has type II diabetes, for which he takes glyburide 5mg twice a day. He has a pleasant demeanor and you learn he is an avid cricket fan.

In your initial investigation, you find that a chest X-ray shows a right upper lobe infiltrate, and sputum microscopy shows 2+ acid fast bacilli. He denies ever having had TB previously. You diagnose Mohan with pulmonary tuberculosis (TB) and decide to initiate him on once-daily treatment with isoniazid, rifampicin, pyrazinamide, and ethambutol (AKT-4). He weighs 53 kilograms at the time of your initial evaluation.

1 **As you start Mohan on TB therapy, what counseling should you provide to counter potential medication adverse effects and to minimize drug-drug interactions, so that he is more likely to adhere and complete therapy?**

a. Advise him that he should not worry if his urine or tears turn red-orange color while on therapy
b. Tell him that his TB medications should only be taken at bedtime
c. Prescribe pyridoxine (vitamin B6) 50mg by mouth daily
d. Advise him to visit his diabetes doctor soon after starting TB therapy, due to a risk of poorer blood sugar control while on TB therapy
e. Both A and C
f. A, C, and D

2 **You see Mohan again more than 6 weeks after starting TB therapy. His weight has dropped from 53kg to 48kg, and he has evidence of temporal wasting. When you talk to him, he endorses ongoing fatigue and night sweats. You worry that he does not seem to be improving clinically after starting TB therapy. What should you do?**

a. Order a GeneXpert MTB/Rif test, line probe assay, or other drug susceptibility testing, if not sent already at the time of diagnosis
b. Carefully screen for poor medication adherence using questions about his pill-taking
c. Empirically add injection streptomycin to his medication regimen
d. Inquire about the quality of his diet and refer him to a dietician
e. Start a rapid prednisone taper
f. A, B, and D
g. A, B, and C

3 **You look in his chart and see that a GeneXpert test sent at the start of therapy was negative for rifampicin resistance. You ask the patient about his medication adherence, and he admits to only taking his TB medications twice in the last week. Upon more careful questioning using the Morisky questions, the patient notes that he experienced some clinical improvement after taking his medications regularly for the first 2 weeks, but then he stopped taking his medications as frequently because he was starting to feel better. He also notes that he often forgets to take his medications due to his busy work schedule and confusion with his diabetes medications.**

What messages can you share with Mohan to ensure that he takes his TB medications every day?

(Questions continued on the next page)

Questions

a. Tell Mohan to stop taking his TB medications if he has acid reflux or mild nausea for the hour immediately after taking his medications
b. Remind Mohan of the consequences of poor medication adherence or stopping TB therapy early, including risk of treatment failure, disease relapse, development of drug-resistant TB, and transmission of TB to family members
c. Recommend that Mohan set a daily alarm on his phone to remind him to take his pills
d. Advise him to stop taking his diabetes medications because curing TB is more important in the short term
e. Advise Mohan to involve his wife or other family members in his care (if he has disclosed his diagnosis to them) to help remind him to take his pills and observe him taking them
f. Ask him to repeat back your instructions about how and when he should take his TB and diabetes medications
g. A, B, and D
h. B, C, E, and F

4 **On follow-up visits for the next two months, Mohan reports improved medication adherence, and his weight increased and symptoms improved. However, he misses his fifth month visit. You call him and Mohan comes into your clinic one week later with his wife. He looks disheveled, does not make eye contact, and provides terse answers during your interview. He smells of alcohol. His wife notes that he becomes intermittently tearful at home and stopped going to work three weeks ago. He stopped taking his TB medications completely at that time.**

What should you do?

a. Tell him that he has finished four and a half months of TB therapy, so it is OK to stop
b. Screen for clinical depression using simple questions and consider referral to a mental health specialist
c. Screen for alcohol use disorder using simple questions and consider referral to a mental health specialist
d. Discuss Mohan's family and social support system with him and his wife
e. B, C, and D

5 **Before the visit is finished, the patient's wife notes that the patient has started drinking alcohol heavily again (around 7 or 8 drinks a day) after years of sobriety and asks for you to provide advice about the patient's alcohol use disorder. What should you advise?**

a. Warn the patient about the increased risk of hepatotoxicity of TB medications when taken with alcohol, and encourage him to contact you quickly for any intractable vomiting or jaundice
b. Identify triggers of his alcohol use (including peer pressure from friends) and recommend strategies for minimizing contacts with these triggers
c. Tell him that he is at fault for his drinking and state that you will no longer see him at follow-up visits unless he stops drinking
d. Advise him to eat before drinking to blunt the effects of the alcohol
e. A, B, and D

(See answers on the next page)

Answers

1 **The correct answer is (F).** Rifampicin often turns body fluids a red-orange color. Alerting patients ahead of time to this benign side effect may help minimize unnecessary concern or interruptions in therapy.

Pyridoxine should be considered for all patients starting TB therapy including isoniazid, but Mohan is at particularly high risk for isoniazid-related peripheral neuropathy due to his diabetes, which can also cause peripheral neuropathy. People living with HIV, malnourished patients, and patients on other medications that can cause peripheral neuropathy (e.g., multidrug resistant TB patients on ethionamide, cycloserine, or linezolid) are also at higher risk for isoniazid-related peripheral neuropathy.

Rifampicin can decrease blood levels of sulfonylureas used to treat diabetes, including glyburide, which can result in worsened blood sugar control in some patients.[1,2] As such, patients on sulfonylurea medications should have their diabetes monitored closely, as they may require modifications of their medications while on TB therapy.

There is no specific requirement that patients should take their TB medications only at bedtime. In general, for patients on standard therapy for drug-susceptible TB, it is important that patients take their medications at the same time every day (whether in the morning or at night). TB medications are best absorbed if taken on an empty stomach; however, for patients with significant gastrointestinal side effects, taking medications with food may be considered to reduce these side effects.

2 **The correct answer is (F).** Ongoing weight loss after weeks of TB therapy should raise concern for potential drug-resistance, poor medication adherence, and poor quality of the patient's diet. Per the Standards for TB Care in India, drug susceptibility testing (DST) should be offered to all diagnosed TB patients prior to starting therapy;[3] however, in cases where DST was not done at the initiation of therapy, failure to respond to therapy as evidenced by ongoing weight loss should prompt GPs to send a DST.

Ongoing weight loss may also suggest that a patient is not taking his or her medications, so screening for non-adherence using simple questions (such as the Morisky questions) is important.

Low caloric intake and poor protein intake may blunt replenishment of the patient's nutritional stores, especially in patients with food insecurity, vegetarian patients with poor protein intake, and patients with a high catabolic state from other comorbidities (e.g., HIV cachexia).

Streptomycin alone should not be added empirically to the patient's medication regimen. If there is high concern for drug-resistant TB, DST should be performed, and empiric multidrug-resistant TB therapy (which would involve addition of multiple medications) can be considered in some cases pending the DST result.

While a prednisone taper might briefly increase the patient's weight and temporarily improve symptoms, it would not improve the patient's long-term response to TB therapy.

3 **The correct answer is (H).** Unfortunately, evidence-based data about the best approaches for ensuring adherence to TB medications are lacking. However, some common-sense strategies for improving medication adherence include improving

(Answers continued on the next page)

Answers

the patient's treatment literacy (by educating about the consequences of non-adherence), setting daily reminders to facilitate pill-taking, involving close family members in the patient's TB care, and implementing a "talk back" strategy at each visit, in which the patient repeats back your recommendations to confirm his or her understanding.

Patients should not stop TB medications for acid reflux or mild nausea, though they should get in touch with their GP. GPs can then check LFTs to rule out hepatotoxicity and recommend therapies to reduce these GI side effects, such as antacids.

Maintaining good glycemic control is important during TB therapy, and patients should not be advised to stop their diabetes medications while on TB therapy.

4 **The correct answer is (E).** Depression and alcohol use disorder are two common barriers to TB medication adherence. Simple questionnaires—such as the Patient Health Questionnaire-2 (for depression) and the AUDIT-C (for alcohol use disorder)—can be easily implemented during brief patient visits to screen for these problems. Ideally, patients should be referred to mental health specialists to help with these problems; however, finding a qualified specialist can be difficult in many areas of India. Encouraging compassionate, non-judgmental involvement from a patient's family members can sometimes provide the social support needed to get through TB therapy.

The patient should not be advised to stop TB therapy, because premature termination of therapy will increase the risk for relapse of TB.

5 **The correct answer is (E).** Patients with alcohol use disorder should be reminded about the increased risk of hepatotoxicity from TB medications. Identifying triggers that lead the patient to use alcohol heavily may help patients to reflect upon how they can avoid these triggers and cut down on drinking. For heavy drinkers, eating before drinking may improve nutritional status and blunt the effects of alcohol.

It is important to have a non-judgmental approach to patients with substance use disorders. Patients are more likely to have ongoing engagement with healthcare providers who are open and compassionate. Recent studies suggest that supportive engagement of patients with alcohol use disorder can improve their TB treatment outcomes.[4]

Nutritional Care and Support of Patients With Tuberculosis in India:

A Primer for General Physicians

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Abstract

Nutritional care is considered fundamental to clinical practice and recognised to be an integral part of TB care, by the WHO and the Revised National Tuberculosis Control Programme(RNTCP). Undernutrition is a comorbidity which is widely prevalent, severe, and persistent even after cure in Indian patients, in the absence of nutritional support. This increases their risk of mortality, drug-induced hepatotoxicity, malabsorption of key drugs like rifampicin, performance status, and relapse even after successful treatment. Providers need to assess weight, height, edema, estimate BMI & measure haemoglobin. BMI < 14 kg/m^2, edema, severe anaemia, inability to stand, are red-flag features which mandate referral for initial inpatient care. Patients should be counselled on an appropriate balanced diet with 3 meals and at least 2 snacks. The RNTCP has evolved food assistance packages consisting of cereals, groundnuts or pulses, milk powder or oil for provision of around 1000 calories and up to 50 gram proteins to patients during treatment, suggests provision of 1 recommended daily allowance of micronutrients and an enhanced quantum of food rations through the public distribution system to TB affected households.

"All doctors should recognize that proper nutritional care is fundamental to good clinical practice."– *Nutrition and patients: A doctor's responsibility.* Report of a Working Party. London: Royal Society of Physicians; 2002.

"Because of the clear bidirectional causal link between undernutrition and active TB, nutrition screening, assessment and management are integral components of TB treatment and care." – *Guideline: Nutritional care and support for patients with tuberculosis.* Geneva: World Health Organisation; 2013.

SOME SCENARIOS OFTEN ENCOUNTERED IN INDIA

Shankar, a manual labourer, diagnosed as extensive smear-positive disease with no other co-morbidity, dies of the disease in the first month of therapy. He weighed just 34 kg with a height of 160 cm. *Laxmi,* another undernourished patient develops jaundice during the first weeks of therapy. *Hamid* who completed treatment successfully as a new case, but weighed 48 kg at the end of regular treatment, developed recurrence of disease after 6 months of stopping it.

It is important to realise that effective chemotherapy is a *necessary prerequisite* but *may not be sufficient* to eliminate the serious adverse outcomes of Mortality, Drug toxicity and Relapse in TB patients. For example, TB mortality in India remains unacceptably high with an estimated 480,000 deaths annually,[1] adverse effects

of medicines was a leading cause of interruption of therapy in India,[2] while the rates of relapse are more than 10% in India, which is twice that considered acceptable (must be <5%).[3,4]

The adverse outcomes in these patients illustrate the interaction between undernutrition and tuberculosis. Undernutrition impairs cell mediated immunity (similar to HIV) which provides protection against TB, and due to its high prevalence in the population, is the major driver of the TB epidemic in India. It contributes to 55% (or more than 1 million cases) of new cases every year.[5] Tuberculosis can itself lead to or worsen pre-existing undernutrition due to its effect on appetite, energy expenditure, and pro-tein catabolism.

The new END TB strategy emphasises integrated patient-centred care, which includes management of co-morbidities, as well as action on risk factors.[6] Undernutrition is a co-morbidity as well as a risk factor for adverse outcomes, which is often neglected.[7] Internationally, the perspective has changed as reflected in the recommendation from a WHO guideline quoted above.[8] The Revised National Tuberculosis Control Programme (RNTCP) has endorsed this changed perspective and released policy guidance on nutritional care and support suitable for the Indian context.[9] This chapter discusses the situation analysis of undernutrition in TB patients, its implications for outcomes in patients, and outlines a nutritional care pathway consisting of assessment, counselling, management and follow up. For more information, the healthcare providers can refer to the RNTCP Guidance Document and the relevant WHO documents.[9-11]

Table 1 — Effect of undernutrition on different outcomes in patients with tuberculosis

Outcome	Effect of undernutrition	Comment
Mortality	Increased risk of death irrespective of age, HIV status or drug-susceptibility status.[23]	BMI approaching 12 kg/m^2 can itself be fatal.[24] Weight less than 50 kg strong predictor of poor outcome in X-DR TB.[25]
Morbidity	Increased severity of disease.	Severe disease increases risk of death, and long-term sequelae
Response to treatment		
• Effect on drug absorption	Sub-therapeutic level of Rifampicin documented[26]	Drug resistance and treatment failure
• Effect on drug metabolism	Increased risk of drug induced hepatotoxicity,[27,28] and other adverse effects[29]	Drug toxicity may lead to interruptions of therapy or default
Relapse	Low BMI and poor weight gain increase the risk of relapse[30]	Poor weight gain in Indian TB patients might be a contributor to higher relapse rates
Performance status	Poor weight gain means poor recovery of lean body mass	Impairment of muscle function could delay return to work and impair work capacity
TB disease in household contacts	Increased risk of disease in undernourished contacts[22] (Grave implications in contacts of patients with MDR-TB/X-DR TB)	Food security is worsened by loss of wages due to TB. Nutritional assessment and support of contacts of MDR-TB especially crucial
Clinical presentation of TB disease	Presentation may be atypical in severely undernourished children or adults	Lower lobe involvement[31] Presentation as an acute pneumonia.[32] A negative tuberculin skin test in undernourished children.

WHAT DO WE KNOW ABOUT THE NUTRITIONAL STATUS OF INDIAN PATIENTS WITH TUBERCULOSIS, AT DIAGNOSIS AND AFTER TREATMENT?

Undernutrition is highly prev-alent, of a serious nature and persists even after successful treatment in patients with TB in India. In a large cohort study in rural patients with pulmonary tuberculosis, half of adult men had a weight below 42 kg, while half of adult women had a weight of less than 34 kg.[12] The reference weights recommended for healthy Indian men and women of 60 kg and 55 kg respectively.[13] In terms of body mass index (BMI calculated as weight in kg/(height in metre squared) half of the adult men had a BMI less than 16.0 kg/m^2, while half of the adult women had a BMI of less than 15 kg/m^2, and BMIs even below 13 were encountered.[12] Nearly three-quarters had anaemia and more than half of the cohort had evidence of chronic undernutrition with stunting.[12] Nationally, the weight data is similar with half of men weighing less than 43 kg and

Table 2 — Tools for nutritional assessment- ABCD

Tool	Basic assessment	Additional assessment and comments
Anthropometry	- Weight, height in all patients - BMI for age/sex in 5-18 years age - BMI in adults - Weight for age z-scores in 0-5 years	Mid upper arm circumference In pregnant women, those with oedema, and those unable to stand
Biochemical and laboratory assessment	- Haemoglobin in all cases - Peripheral smear in case of anaemia	Serum electrolytes required in severe undernutrition.
Clinical assessment	- Pallor - Loss of buccal pad of fat - Oedema on feet and legs suggesting hypoproteinaemia - Wasting of muscles	Flaky skin, sparse pluckable hair with depigmentation especially is seen in under-5. Bitot's spots and glossitis suggest vitamin deficiencies
Dietary assessment	- Appetite - Intake over past few days - Food preferences: vegetarian or non-vegetarian	Food availability and diversity at household level. Access to supplementary nutrition programmes

women weighing less than 38 kg.[14] Micronutrient deficiency is also common in patients with active TB with iron and folate, vitamin A, zinc, vitamin D deficiencies.[15-17] Only one third of the men and a quarter of the women in the rural cohort, had BMIs in the normal range after cure.[12] Half of rural patients with active TB gained less than 3.9 kg,[18] which is similar to patients under the RNTCP, about 3.2 kg.[19] These are clearly suboptimal, while an optimal diet provided in the famous Madras trial resulted in much higher weight gains.[20]

WHAT ARE THE IMPLICATIONS OF UNDERNUTRITION IN PATIENTS WITH TB?

Undernutrition affects occurrence of TB, its severity, its outcome during and after treatment. It may also influence clinical presentation of disease.

Link between undernutrition and occurrence, severity of TB

Undernutrition is not only a risk factor for tuberculosis, but also makes the disease severe, which in turn worsens the undernutrition. As stated in a WHO guideline *"without nutritional support, patients, especially those already suffering from baseline hunger, can become enmeshed in a vicious cycle of malnutrition and disease"*.[18] This can even result in death. Food insecurity has a strong association with risk of TB in contacts and undernutrition in household contacts increases the risk of active TB in them.[21, 22]

Link between undernutrition and outcomes in TB

Undernutrition at diagnosis in a patient with active TB can increase the risk of unfavourable outcomes. These are listed in **Table 1.**

WHAT ARE THE FOOD-DRUG INTERACTIONS WITH FIRST-LINE ANTI-TB DRUGS? SHOULD ISONIAZID ALSO BE TAKEN IN FASTING STATE?

Rifampicin is usually advised to be taken on an empty stomach for better bioavailability. It is advisable to give other medicines like isoniazid also in the fasting state.[33] Recent studies have shown that food decreased the peak concentrations of isoniazid and rifampicin in the range of 20 to 40%.[34,35] This lowering of serum levels of first-line drugs with food can impact treatment outcomes,[36] and may be of particular importance in undern-ourished patients who may have lower levels of rifampicin.[26] Physician often advise anti-TB drugs after meals when patient have gastrointestinal side effects. In such a case, it is advisable to take them 2-3 hours after a meal.[37] Antacids or H_2 blockers do not affect drug absorption, and may also be tried.[33] Drugs like Isoniazid can cause pyridoxine deficiency which can lead to peripheral neuropathy. This effect can be prevented by giving pyridoxine 10 mg per day, and this is especially important in undernourished individuals.

WHAT ARE THE STEPS IN THE NUTRITIONAL CARE PATHWAY?

The steps in the nutrition care pathway consist of nutritional assessment, nutritional counselling, and nutritional support and follow up. The physician should also take into account any other co-morbidities of the patient

Table 3 — BMI based cut-offs suggested for nutritional classification

BMI (Kg/m²)	Classification
<14.0	Extremely underweight
<16.0	Grade III underweight
16.0 – 16.9	Grade II underweight
17.0 – 18.4	Grade I underweight
18.5 – 24.9*	Normal weight

*A WHO expert consultation in 2004 proposed different cut-offs for overweight and obesity in Asians. The different cut-offs for obesity are not mentioned here as this is less likely to be encountered in TB cases

e.g., diabetes which have their own implications for nutritional counselling and therapy

Nutritional assessment

The tools for nutritional assessment can be classified as ABCD **A**nthropometry, **B**iochemical assessment, **C**linical Assessment, and **D**ietary assessment summarised in **Table 2.**

The RNTCP guidance document has suggested the following red-flag features related to nutritional status which indicate need for patient care as indicated in **Box 1.**[9]

Nutritional assessment of con-tacts. The WHO recommends nutritional screening and screening of contacts of TB patients followed by management of undernourished contacts as per the guidelines.[8] Recent changes in weight may be a symptom of disease in contacts, while chronic undernutrition in those without disease, (especially children) should be addressed to decrease their risk of developing active TB.

**A desirable body weight is one which corresponds to the BMI of 20-22 kg/m². See[9] for details.*

Nutritional counseling

The WHO guidelines recommend as a principle that "an adequate diet, containing all essential macro- and micronutrients, is necessary for the well-being and health of all people, including those with TB infection or TB disease".[8]

The requirements of an adequate diet for a patient with active TB in India are as follows:[9]

- Approximately 40 kcal/kg of ideal or desirable body weight;*
- Proteins should be 1.2-1.5 gm/ ideal or desirable body weight;
- Fat requirements are similar to general population;
- Micronutrient requirement is sim-ilar to general population. One daily allowance in the form of a multivitamin supplement is reco-mmended.

Patients of TB in India, especially the poor, may not be able to meet their requirement for a healthy balanced diet and may require nutritional support. In a study the mean calorie intake in patients with TB and HIV was in the range of 1545-2016 calories per day, and was similar to the HIV negative community controls.[38]

The practical points to be emph-asised during nutritional counselling are as follows:

Balanced diet. One which has adequate proportion of foods from all the food groups:

-Cereals, millets and pulses
-Vegetables and fruits
-Milk and milk products, meat, eggs and fish
- Oils, fats, nuts and oil seeds

Ask about preferences– vegetarian vs. non-vegetarian. Vegetarians can get adequate protein of good quality by combining cereals with pulses, and by consuming milk and milk products.

Emphasise cost-effective locally available options in the food groups. Local cereals including millets, local pulses, and local fruits may offer good nutrition at lower cost. Egg protein is better compared to even proteins from fish and meat, while eggs are also cheaper. Groundnuts are a good source of calories and proteins, and equivalent to dry fruits. They should be eaten preferably roasted and with skin removed.

Emphasise frequent feedings 3 meals + at least 2 snacks for nutritional recovery. Increase caloric value of meals by adding ghee (if available) or oil to rice or chapatti. Snacks may be fruits (e.g., bananas), groundnuts, chikki, laddu, roasted horse-gram.

Address misconceptions. Comm-ercial supplements provide the same nutrients at higher cost. A 200 gm tin of protein supplement costing around Rs. 175 has 40 gm protein, which can also be obtained in 1200 ml milk or 6 eggs, or 200 gm pulses. Tonics are not useful nor are IV drips.

Recommend hygiene. Recommend food hygiene, hand washing and good cooking practices.

Recommend referral. Recommend referral for patients with red-flag features on nutritional assessment **(Box 1).**

Contacts, especially young children who are undernourished can be referred to appropriate nutritional assistance services like ICDS services, nutritional

Box 1 – Red-flag features on nutritional assessment

1. BMI of 14.0-15.9 kg/m² with no appetite OR bilateral oedema OR inability to stand, OR
2. BMI of less than 14 kg/m², OR
3. Haemoglobin of less than 7 gm/dl.

rehabilitation centres.

The annexures in the RNTCP document contain dietary requirements, exchange lists, sample meal plans and model diets for patients with tuberculosis.[9]

Nutritional support

Patients with undernutrition can be managed on an individualised basis with calculation of their energy and protein requirements. A food assistance package has been proposed which can serve the needs of individual patients and TB programmes. This is based on the pattern of weights in India, and is intended for all patients with active TB (irrespective of HIV status, drug-susceptibility status).

The RNTCP guidance document has also suggested a food assistance package for all patients with active TB which consists of the following:[9]

1. A food assistance package for the patient of 5 kg cereal (rice, wheat, millet) along with 1.5 kg milk powder and 3 kg groundnuts (preferably roasted and skinned). The other accompanying options with the cereal are 3 kg groundnuts and 1 kg oil OR 3 kg pulses and 1 kg oil. This would ensure provision of around 1000 calorie and up to 52 g protein per day;
2. A multivitamin tablet containing one recommended daily allowance of all micronutrients;
3. In addition, the RNTCP guidance document recommends doubling the PDS ration for the family to address food insecurity and provides an additional 500 calories for family members and the patient.

This form of nutritional support would ensure that patients are able to meet their usual requirement of calories and proteins and the 312-625 calories/day, they require in addition to recover the lost weight.

Inpatient nutritional care and support for patients with red-flag features. A certain proportion of patients with tuberculosis in India like Shankar mentioned earlier, have red-flag features at diagnosis. Shankar's BMI for example was 13.28 kg/m^2, indicating high risk of complications including early mortality. Such patients should be treated as inpatients for initial 1-2 weeks. The management of such patients is discussed in the RNTCP guidance document as well as a WHO manual.[8,9] Briefly, the patient requires stabilisation of fluid, electrolyte status, and initiation of feeding in gradually increasing amounts in the first week. No weight gain should be expected in this initial phase. Patients will require supplementation with potassium and magnesium, thiamine and B-complex vitamins orally.[39] A potentially lethal complication of nutritional support-the refeeding syndrome, can occur if the refeeding is not cautious. This syndrome can manifest as life-threatening cardiac arrhythmias, severe electrolyte disturbances, neurological complications and hyperglycaemia.[39] The risk factors for refeeding syndrome are–patients with BMI less than 16 kg/m^2, those with low potassium, magnesium prior to refeeding, and those who consume alcohol.[39] In the second week, once the patient has stabilised, the appetite has improved, and the patient begins to gain weight, he can be discharged.

Nutritional monitoring during follow up

Nutritional indices appropriate to the age group like BMI and weight or weight for age should be monitored monthly or at least at 2, 4 and 6 months of follow-up. A weight gain of at least 5% of baseline in the first 2 months should be the target, and a BMI of 21 kg/m^2 would be optimal.

Poor weight gain or occurrence of weight loss should be investigated. The possible causes can be treatment failure, non-adherence to therapy, food insecurity and inadequate dietary intake, or drug-induced hepatotoxicity.

NUTRITIONAL SUPPORT: A BRIEF REVIEW OF THE EVIDENCE IN PATIENTS WITH TUBERCULOSIS

The evidence surrounding nutritional support lacks firm conclusions primarily due to the limited numbers of studies done with macronutrient supplementation which had inadequate sample sizes, as well as inability to achieve recommended dietary intakes. There is also an ethical issue about conducting RCTs on undernourished patients without providing them nutritional support. There is robust data from other fields on the effect of nutritional support on mortality. For example, management of severe acute malnutrition in children can reduce case-fatality by 55%.[40]

The old and emerging evidence related to nutritional support is clini-cally and programmatically important. The benefits include 1.6-2 times higher weight gain,[20] shorter time to sputum conversion and sustained microbiological cure,[41] improvements in muscle strength,[42] improved pha-rmacokinetics of rifampicin,[43] promising reduction of TB related mortality [Risk ratio: 0.18(0.02,1.48)] in preliminary studies from India,[44,45] 50% reduction in unfavorable outcomes and improved adherence in the supplemented group in a

programmatic setting in India.[46] Adequate weight gain was associated with a two fold higher odds of treatment successes in MDR-TB patients.[47] Finally, at the Papworth village settlement for the TB affected, social interventions of which adequate nutrition was considered the most important, reduced six-fold the incidence of TB in contacts which included young children, even when the patients had no access to TB drugs, and the contacts who were uniformly infected by the age of five years, and had not been vaccinated.[48]

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CIS CME–Questions

Nutritional Care and Support of Patients With Tuberculosis in India: A Primer for General Physicians

Questions

1 Which of the following is true of undernutrition and TB?

a. Undernutrition is a risk factor for TB
b. Tuberculosis can lead to undernutrition
c. Undernutrition worsens severity of tuberculosis
d. Undernutrition is associated with adverse outcomes in TB patients
e. All of the above

2 A patient with a height of 170 cm has a weight of 45 kg. His calculated BMI would indicate

a. Normal body weight
b. Mild undernutrition
c. Severe undernutrition
d. Moderate undernutrition

3 Which of the following drug/s should be given on an empty stomach for better bioavailability.

a. Isoniazid
b. Rifampicin
c. Ethambutol
d. Isoniazid as well as rifampicin

4 A labourer with TB has signs of hypoproteinaemia. What would be an appropriate dietary advice?

a. Take 4 teaspoons of a commercial supplement, which has 40 gm protein in 200 gms
b. Eat mutton, chicken (if he is non-vegetarian)
c. Eat additional quantity of pulses or eggs (if he is non-vegetarian)
d. Take 2 tsp of a tonic containing amino acids daily

5 Pyridoxine deficiency can occur due to treatment of which anti-TB drug?

a. Rifampicin
b. Isoniazid
c. Ethambutol
d. Pyrazinamide

6 The following are true for inpatient care of patient with red-flag features in the first week, except

a. Feed vigorously with the daily requirement of calories and protein
b. Give adequate quantities of potassium, magnesium
c. Correct dehydration
d. Give thiamine and B-complex vitamins during this phase

(See answers on the next page)

CIS CME–Answers

Nutritional Care and Support of Patients With Tuberculosis in India: A Primer for General Physicians

Question on the previous page

Answers

1. **The correct answer is (e).**

2. **The correct answer is (c).** BMI is calculated as weight in kg/(height in metre).^{2} The BMI in this patient would be 45/(1.7)^2= 15. 57 kg/m^2. This is less than 16.0 kg/m^2 and indicates severe undernutrition.

3. **The correct answer is (d).** The bioavailability and peak serum concentrations of both isoniazid and rifampicin is affected by food.

4. **The correct answer is (c):** The commercial protein supplement may contain 40 gm protein in a 200-gm pack, but is costly and inappropriate, as are tonics with amino acids. Mutton and chicken are more expensive than eggs and the labourer is more likely to afford additional pulses or eggs, than eat chicken or mutton on a daily basis. The protein content per 100 gm, does not differ between eggs and chicken.

5. **The correct answer is (b).** Isoniazid interferes competitively with pyridoxine metabolism by inhibiting the formation of the active form of the vitamin, and hence often results in peripheral neuropathy. This is especially marked in malnutrition, pregnancy, lactation, HIV infection, diabetes and hypertension. This effect can be prevented by giving pyridoxine 10 mg per day.

6. **The correct answer is (a).** In a patient with very low BMI and who has probably been eating little for many days, vigorous feeding may result in refeeding syndrome which can be dangerous. The feeding should start at 50% of the dietary requirement or even lower in the first few days, along with the other measures mentioned.

India's Ambitious New Plan to Conquer TB Needs Cash and Commitment

Madhukar Pai, MD, PhD—Author and Series Editor

TUBERCULOSIS (TB) KILLS MORE PEOPLE TODAY THAN HIV AND MALARIA COMBINED.

In 2016, there were an estimated 10.4 million new TB cases worldwide and 1.7 million TB deaths, according to the World Health Organization. And India is at the epicentre of this global epidemic, with half a million TB deaths annually. India also accounts for 16 per cent of the estimated 490,000 new cases of multi-drug-resistant TB.

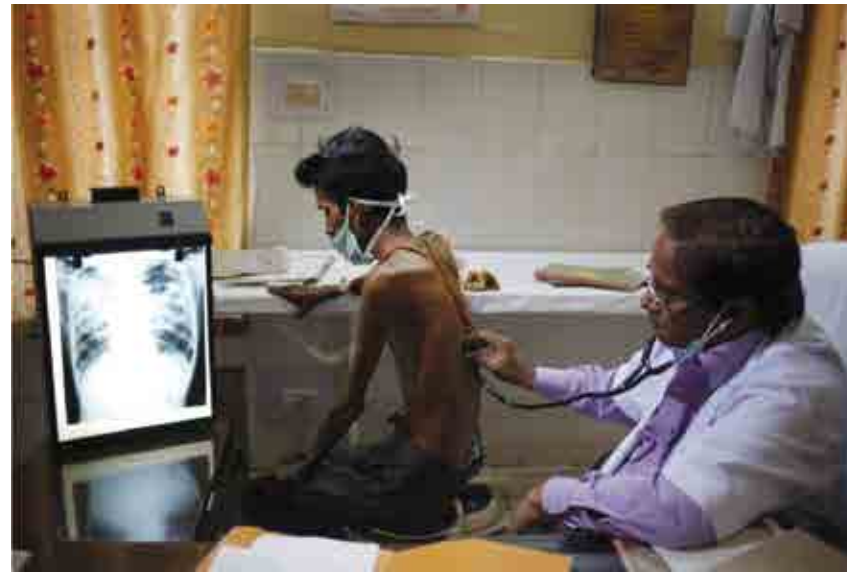
CAN INDIA TURN THINGS AROUND AND CONTROL THIS EPIDEMIC?

The answer is a conditional yes. The Indian government has already taken several steps over the past few years to address it. This includes making TB a notifiable disease, developing the Standards for TB Care in India, introducing daily drug regimens and rolling out molecular and drug-susceptibility testing.

But there's an opportunity to do more and better, and for India to assume a global leadership role.

INDIA MUST BACK AMBITIONS WITH RUPEES

Earlier this year, India's Revised National TB Control Program published a draft of a new National Strategic Plan (NSP) for TB Elimination 2017-2025. The NSP, if



Tuberculosis alone kills an estimated 480,000 people in India every year, according to the World Health Organization's Global Tuberculosis Report 2016. (AP Photo/Rajesh Kumar Singh)

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Link to the article: https://theconversation.com/indias-ambitious-new-plan-to-conquer-tb-needs-cash-and-commitment-84821

India's Ambitious New Plan to Conquer TB Needs Cash and Commitment

A tuberculosis patient sits in the sun with her mother outside Lal Bahadur Shastri Government Hospital at Ram Nagar in Varanasi, India. (AP Photo/Rajesh Kumar Singh)

fully funded and well implemented, could be a game changer in the fight against TB in India.

The plan aims to improve services and outcomes for the 1.5 million patients in the public system and to scale up access to new diagnostics and drugs. It also sets out a bold road map to reach private providers and support the millions of patients treated in the private sector.

Building on promising pilot results, the NSP proposes to do so by providing incentives to providers — for following standard protocols for diagnosis and treatment as well as for notifying the government of cases. Patients referred to the government will in turn receive a cash transfer, to compensate them for direct and indirect costs of undergoing treatment and as an incentive to complete treatment.

The cost of implementing the new NSP is estimated at US$2.5 billion over the first three years, a big increase over the current budget. Historically, despite being a highly cost-effective program and despite having a high absorptive capacity, RNTCP has struggled to receive funding that is commensurate with the scale of India's epidemic.

This simply cannot continue. India must start backing its ambitions with rupees. Therefore, the real test of whether the bold plan by the Health Ministry can be implemented will be whether enough resources can be mobilized — to find, treat and offer quality care to all TB patients, regardless of where they live.

HEALTH SPENDING AN URGENT PRIORITY

TB is one of many diseases that affect Indians, and India is clearly under-performing on several key health indicators, as shown by a recent report on attainment on health-related Sustainable Development Goals (SDGs) in 188 countries. This is an analysis from the Global Burden of Disease Study 2016, which measured 37 health-related indicators from 1990 to 2016.

India did very poorly in this analysis, ranking 127 among 188 countries. In fact, every single other BRICS country (Brazil, Russia,

China and South Africa) ranked ahead of India.

This analysis clearly shows that India's economic progress is not reflected in the health of its people. India's National Health Policy, approved this year, proposes to increase health expenditure by the government from the existing 1.15 per cent to 2.5 per cent of the GDP, by 2025.

Ensuring this increase should be an urgent priority for India, and an absolute requirement if India is to make progress towards universal health coverage.

A TRADITION OF EXCELLENCE

Are there areas of strength that India can leverage to fight TB?

India has made some impressive contributions in global health. India has been polio-free for more than five years and this success has propelled global efforts to eradicate polio. Indian biotech and drug manufacturers dominate the production of TB and HIV medications, accounting for more than 80 per cent of the global market.

The recent launch of a rotavirus vaccine produced in India has underscored the country's leadership role in childhood immunization. India also has huge strengths in IT and software that can be leveraged. And India has a long tradition of excellence in TB research, highlighted by the creation of an India TB Research Consortium.

So, with its strong research expertise in TB, and technological and pharmaceutical capacity, India has the potential to make great progress against this disease.

What is essential is a strong financial and political commitment from Prime Minister Narendra Modi to end the TB epidemic, and an overall greater investment in health. When health becomes a priority for India, TB will naturally decline, as will many other conditions that currently make India rank so poorly in health-related SDGs.

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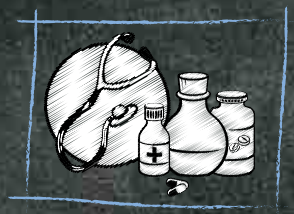
Municipal Corporation of Greater Mumbai

MUMBAI MISSION FOR TB CONTROL

Being careless will not help you win the battle against TB



- Avoid delay in diagnosis
- Get your sputum examined
- Take your TB medication regularly
- Complete the full course of treatment to avoid complications

TB HAREGA, DESH JEETEGA.

For more information, consult your doctor.

ABOUT REACH

REACH joined the fight against Tuberculosis (TB) in 1999, as a non-profit organisation based in Chennai in South India. In the 15 years since, REACH has worked as an interface between the public health system and private healthcare providers and adopted a holistic approach to the diagnosis and treatment of TB. A comprehensive patient care system is at the heart of our work, designed to ensure that those affected by TB receive the support they deserve.

INITIATIVES BY REACH

REACH conceptualized, implemented and monitored an innovative public private partnership model for engaging private practitioners (PPs). As an intermediary between the Chennai Corporation and private providers, REACH identified private hospitals and clinics to function as PPM (Public Private Mix) centres. REACH assisted the PPM centres by obtaining patient-wise drug boxes and TB registers from the Chennai Corporation for use at these centres. REACH also identified and trained community volunteers for DOTS and provided support for patient follow up and documentation. Through this model, REACH demonstrated that access to RNTCP services could be increased for private patients and that it was possible to engage PPs in TB control efforts. More than 2000 PPs were sensitized through workshops and one-to-one visits. REACH also provides a continuum of care including patient support, nutrition, family support and transport with a special focus on the poor and vulnerable, homeless, migrant workers and daily wage earners.

In addition, since 2010, with support from the Lilly MDR-TB Partnership, REACH has trained nearly 700 private pharmacists in Chennai and engages them in a sustained manner. Trained pharmacists refer those with TB symptoms for testing and occasionally function as DOTS providers themselves. REACH is currently implementing Project Axshya, in 14 districts of Tamilnadu to synergize TB control efforts with government, private sector and communities through civil society groups. Through this project, REACH has trained NGOs to create awareness about the disease in the community and identify and link those with TB symptoms to government TB services. The REACH Lilly MDR-TB Partnership Media Initiative began in 2010 to improve the quality and frequency of media reporting on TB, particularly among local language media.

REACH continues to closely with the public health system and the Revised National TB Control Program, increasing referrals, promoting treatment adherence and supporting patients through the treatment process.

We would be happy to receive your feedback or comments at reach4tb@gmail.com
For more information, visit www.reachtbnetwork.org

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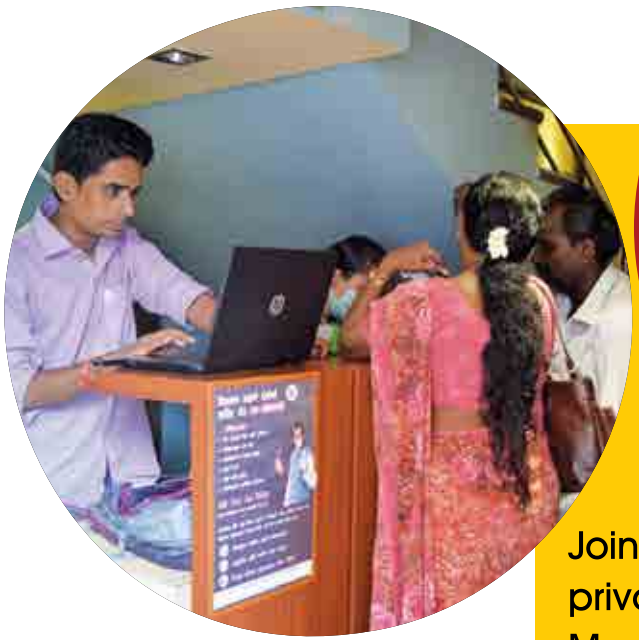

Private Provider Interface Agency

Join the proud network of around 2400 private practitioners to conquer TB in Mumbai. CALL NOW!

9820504864

We are PPIA

The Private Provider Interface Agency (PPIA) is to engage with the private sector for timely diagnosis and treatment of tuberculosis in Mumbai. PPIA has partnered with local NGOs, private providers, including MD, MBBS, and AYUSH practitioners, laboratories, hospitals, and chemists in high TB-risk and high slum population wards in Mumbai.

We provide services

1. Free digital chest X-ray along with CBC and ESR test of suspected TB cases
2. Subsidized geneXpert MTB/Rif test at IPAQT labs and bringing the cost to patient down from INR 2000 to INR 250 per test.
3. Provision for sputum sample collection and transportation for geneXpert MTB/Rif test.
4. Facilitating TB case notification into Nikshaya.
5. Free first-line anti-TB drugs at private pharmacies and chemists for a duration of up to 9 months.
6. Counselling support to privately diagnosed TB patients on treatment adherence and follow up.
7. SMS and reminders by call center to encourage patients to continue treatment.

Please join us

For more information call on

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Email: ppiamumbai@path.org

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WHO ENDORSED DIAGNOSTIC ALGORITHM FOR TB DIAGNOSIS

PATIENTS POSING SYMPTOMS OF TUBERCULOSIS


>2 WEEKS OF COUGH


FEVER


WEIGHT LOSS


TIREDNESS


NIGHT SWEATS


LOSS OF APPETITE

*Xpert MTB/RIF may be used as the initial diagnostic test in all adults and children who are at risk of TB.

1 MICROSCOPY

NEGATIVE

If TB is clinically suspected

2 *GENEXPERT MTB/ RIF ASSAY

POSITIVE

TB RIF RESISTANCE

TB, Susceptible

No TB

No Result

2 LINE PROBE ASSAY

MDR TB

TB MONORESISTANT TO INH & RIF

TB, Susceptible

No TB

No Result

3 AFB CULTURE

3 DST FOR FIRST AND SECOND-LINE AGENTS

Adapted from WHO Implementing Tuberculosis Diagnostics Policy Framework 2015 Section 9- Algorithms for diagnostic testing Pg 24-29

TB affects around 28 lakh people annually in India and each undiagnosed and wrongly diagnosed case may spread the disease in their family and community. Approximately 3% new TB patients may have Multi-Drug Resistant (MDR) strains of TB; amongst patients who had been treated for TB before, about 12-17% may have MDR- TB. Earlier antibody tests were popular in the private sector, but these tests have proved to be inaccurate and hence banned by the Government of India. Blood-based tests like IGRAs* could be helpful in detecting latent TB infection, but are not useful for diagnosing active TB. There has always been a need to rely on affordable and accurate tests *i.e.* those endorsed by the WHO and the RNTCP and Standards for TB Care in India (STCI).

IPAQT Partner laboratories in India offer WHO endorsed tests for TB diagnosis at substantially reduced prices. You can now get your patients tested for TB and MDR-TB and get results quickly through molecular tests which offer high accuracy and are available through a network of quality assured laboratories.

	Test	Sample Type	Turn around Time	Sensitivity	Specificity	Ceiling price under IPAQT
	LED Microscopy	Pulmonary	1 day	70%	>90%	₹ 500
	Hain LPA	Pulmonary	2-3 days	98%	99%	₹ 1800
	GeneXpert	Pulmonary & EPTB Samples	1 day	96%	99%	₹ 2200
	MGIT	Pulmonary & EPTB Samples	8-14 days	Gold Standard	Gold Standard	₹ 900
	BacT/Alert	Pulmonary & EPTB Samples	8-14 days	Gold Standard	Gold Standard	₹ 900

ABOUT IPAQT

IPAQT is an initiative of non-profit stakeholders and over 150 private sector labs/hospitals (and more than 5000 collection centers) with a pan-India presence that have come together to provide WHO approved tests for TB at the lowest price to patients seeking care in the private sector.

TO FIND A LAB NEAR YOUR THAT IS PART OF IPAQT, PLEASE LOG ON TO : www.ipaqt.org

IPAQT

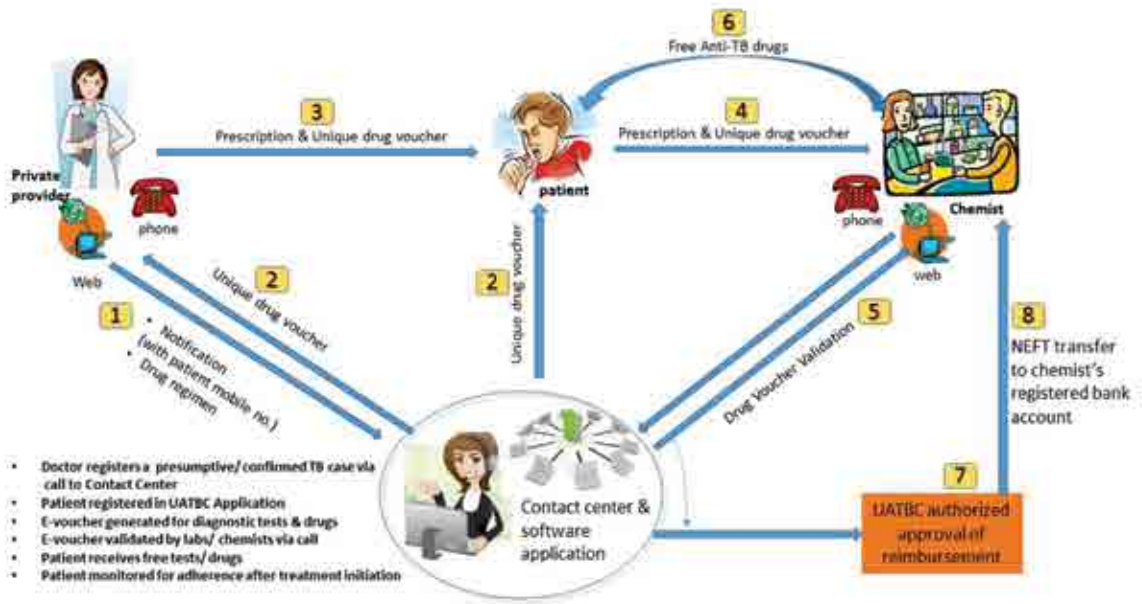
INITIATIVE FOR PROMOTING AFFORDABLE AND QUALITY TB TESTS

Universal Access to Tuberculosis Care

Program objectives

- Facilitate early and accurate diagnosis of TB in the private sector in urban Patna
- Facilitate notification of cases diagnosed and treated in the private sector
- Ensure appropriate treatment of cases in the private sector as per national Standards for TB Care
- Ensure treatment completion and improved cure rates of TB patients in the private sector

PPIA Model



Services offered

- Free Sputum Microscopy
- Subsidized GeneXpert/ CBNAAT
- Free Chest X-Ray
- Free anti –TB drugs
- Counseling on Cough Hygiene and Adherence

GeneXpert/ CBNAAT

Call Centre

Activities for mobilizing the community

Community meetings

Health camps

Outdoor Advertising

A TB helpline number (08010108080)

Progress

- Doctors engaged- 615
- Informal providers engaged - 786
- Chemists - 663
- Labs and X Ray units- 140
- TB notification- 14138
- Patients on free drugs -12439
- Treatment completed- 1827

Universal Access to TB Care
TB Free India - Nikshay
Standards for TB Care in India

For more details visit

www.worldhealthpartners.org

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FIND

Because diagnosis matters

Why diagnostics?

Diagnosis is the first step on the path to treatment and renewed health. Diagnostics guide the most effective health care interventions, measure treatment progress and improve the efficiency of health care spending. Diagnostics are the foundation of disease surveillance and elimination and aid in the fight against the development of antimicrobial resistance by guiding the appropriate use of antibiotics.

Accurate diagnosis saves lives.

But not everyone has access to diagnosis for some of the most devastating diseases affecting their communities – either because the right diagnostic tools have not yet been developed or because they are not available where people live and work. FIND is working to change that.

> *Without diagnostics, medicine is blind.*
>
> Dr Alain Mérieux
> President, Fondation Mérieux
> & diagnostics pioneer

Why FIND?

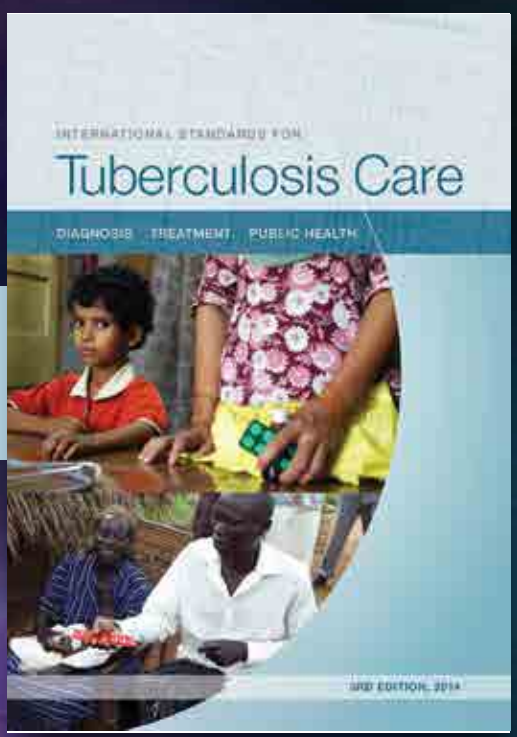
FIND, a global non-profit organization, was founded to bridge gaps in research and development (R&D) of essential diagnostics for diseases of poverty, and now also focuses heavily on the delivery of these diagnostics in low- and middle-income countries.

At FIND, we work through partnerships with the international research community, the public sector and the diagnostics industry. We create an enabling environment for diagnostics R&D by providing specimen banks, trial sites to evaluate new tests and better market visibility for new tools. Once tests have been evaluated and approved, we work with partners to turn a diagnostic *test* into a diagnostic *solution*…by supporting the development of new health policies, training and mentoring lab technicians and clinicians, and ensuring there are systems in place to maintain the quality of newly introduced tests.

Through our programmes in tuberculosis, sleeping sickness and malaria, we have already delivered 11 tests in 12 years and helped transform the diagnostics landscape for each of these disease areas. Other programmes include hepatitis C, HIV/AIDS, leishmaniasis, Chagas disease and Buruli ulcer. FIND is also working in areas that cut across many diseases – including diagnostics for diseases with outbreak potential, such as Ebola; connecting diagnostics to digital technology to improve patient care and disease surveillance; and helping to accelerate access to new diagnostic tools that will make a difference in the fight against antimicrobial resistance, such as a rapid test to distinguish between bacterial and non-bacterial infections.

For additional guidance on TB diagnosis and management, please see these documents that are available free:

Standards for TB Care in India, 1st Edition, 2014
URL: http://www.tbcindia.nic.in/pdfs/STCI%20Book_Final%20%20060514.pdf



International Standards for TB Care, 3rd Edition, 2014
URL: http://www.istcweb.org/Home.html

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